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(54) **CYCLIC HYDRAZINE DERIVATIVES AS HIV ATTACHMENT INHIBITORS**

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A61K 31/519	(2006.01)
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CPC ***C07D 471/04*** (2013.01); ***A61K 31/501*** (2013.01); ***A61K 31/519*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 519/00*** (2013.01)

(58) **Field of Classification Search**

CPC C07D 471/04
USPC 544/236, 238
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,413,999	A	5/1995	Vacca et al.
7,348,337	B2	3/2008	Wang et al.
7,354,924	B2	4/2008	Wang et al.
7,396,830	B2	7/2008	Wang et al.
7,504,399	B2	3/2009	Wang et al.
7,745,625	B2	6/2010	Ueda et al.
7,776,863	B2	8/2010	Lin et al.
7,851,476	B2	12/2010	Chen et al.
2005/0215543	A1	9/2005	Lin et al.
2005/0215544	A1	9/2005	Lin et al.

FOREIGN PATENT DOCUMENTS

EP	0484071	5/1992
WO	WO 02/62255	8/2001
WO	WO 02/062423	8/2002
WO	WO 03/103607	12/2003
WO	WO 2005/016344	2/2005
WO	WO 2005/121094	12/2005
WO	WO 2007/103456	9/2007
WO	WO 2009/158396	12/2009

OTHER PUBLICATIONS

Plieninger et al. STN Abstract of Chemische Berichte (1960), 93, 2024-8.*

Blair, W.S. et al, "HIV-1 entry—an expanding portal for drug discovery," Drug Discovery Today, vol. 5, No. 5, pp. 183-194 (May 2000).

Carpino, L.A. et al, "Advantageous Applications of Azabenzotriazole (Triazolopyridine)-based Coupling Reagents to Solid-phase Peptide Synthesis," J. Chem. Soc., Chem. Commun., pp. 201-203 (1994).

El-Desoky, S.I. et al., "Synthesis of Pyrrolo-, Thienopyrrolo-, Benzothienopyrroloquinolines as well as Triazoloindole Derivatives," Z. Naturforsch. 53b, pp. 1216-1222 (1988).

Hotoda,H., "Small-molecule inhibitors of HIV-1 entry via chemokine receptors," Drugs of the Future, 24(12), pp. 1355-1362 (1999).

Kumar, P. et al, "Antiparasitic agents: Part XI-Synthesis and anthelmintic activity of 6-/8-[(2-carbomethoxyamino)benzimidazole]-5-carbonylamino-1- substituted-9*H*-pyrido[3,4-*b*]indoles," Indian Journal of Chemistry, vol. 29B, pp. 1077-1080 (Nov. 1990).

Li, H. et al., "3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT): A New Coupling Reagent with Remarkable Resistance to Racemization," Organic Letters, vol. 1., No. 1, pp. 91-93 (1999).

Lu, R.-J. et al, "Design and Synthesis of Human Immunodeficiency Virus Entry Inhibitors: Sulfonamide as an Isostere for the α-Ketoamide Group," J. Med. Chem., 50, pp. 6535-6544 (2007).

Maklakov, S.A. et al, "Synthesis of N-Substituted Derivatives of (5-amino-2- methy1-1H-indo1-3-yl)acetic acid," Chemistry of Heterocyclic Compounds, vol. 38, No. 5, pp. 539-542 (2002).

Meanwell, N.A. et al, "Inhibitors of the entry of HIV into host cells," Current Opinion in Drug Discovery & Development, 6(4), pp. 451-461 (2003).

Sodroski, J.G., "HIV-1 Entry Inhibitors in the Side Pocket," Cell, vol. 99, pp. 243-246 (Oct. 29, 1999).

Takeuchi, Y. et al, "Synthesis and Antitumor Activity of Fused Quinoline Derivatives. III. Novel *N*-Glycosylamino-indolo[3,2-*b*]quinolines," Chem. Pharm. Bull., 40 (6), pp. 1481-1485 (1992).

Virgilio, A.A. et al., "Simultaneous Solid-Phase Synthesis of β-Turn Mimetics Incorporating Side-Chain Functionality," J. Am. Chem. Soc., 116, pp. 11580-11581 (1994).

Wang, J. et al, "Modification and structure-activity relationship of a small molecule HIV-1 inhibitor targeting the viral envelope glycoprotein gp120," Org. Biomol. Chem., 3, pp. 1781-1786 (2005).

* cited by examiner

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(57) **ABSTRACT**

Compounds of Formula I are provided, including pharmaceutically acceptable salts thereof: wherein A is selected from the group consisting of: wherein Z is selected from the group consisting of: which are useful as HIV attachment inhibitors.

7 Claims, No Drawings

CYCLIC HYDRAZINE DERIVATIVES AS HIV ATTACHMENT INHIBITORS

FIELD OF THE INVENTION

This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use. In particular, the invention herein is directed to cyclic hydrazine derivatives as HIV attachment inhibitors that possess unique antiviral activity.

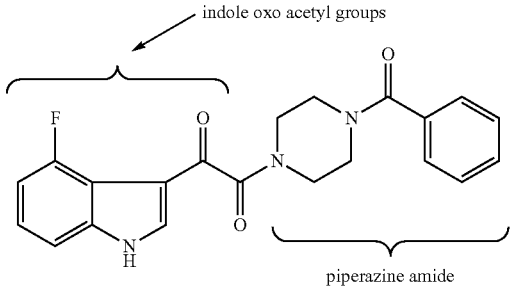
BACKGROUND OF THE INVENTION

HIV-1 (human immunodeficiency virus-1) infection remains a major medical problem, with an estimated 45 million people infected worldwide at the end of 2007. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors zidovudine (or AZT or RETROVIR®), didanosine (or VIDEX®), stavudine (or ZERIT®), lamivudine (or 3TC or EPIVIR®), zalcitabine (or DDC or HIVID®), abacavir succinate (or ZIAGEN®), tenofovir disoproxil fumarate salt (or VIREAD®), emtricitabine (or FTC-EMTRIVA®); non-nucleoside reverse transcriptase inhibitors: nevirapine (or VIRAMUNE®), delavirdine (or RESCRIPTOR®), efavirenz (or SUSTIVA®), etravirine (INTELENCE®) and rilpivirine (EDURANT®), and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, KALETRA® (lopinavir and Ritonavir), darunavir, atazanavir (REYATAZ®) and tipranavir (APTIVUS®), and integrase inhibitors such as raltegravir (ISENTRESS®), and entry inhibitors such as enfuvirtide (T-20) (FUZEON®) and maraviroc (SELZENTRY®). Several single pill combinations have been also approved, which include COMBIVIR® (contains lamivudine and zidovudine), TRIZIVIR® (contains abacavir, zidovudine, and lamivudine), Epzicom® (contains abacavir and lamivudine), TRUVADA® (contains tenofovir disoproxil fumarate and emtricitabine), ATRIPLA® (contains efavirenz, emtricitabine and tenofovir disoproxil fumarate) and COMPLERA® (contains emtricitabine, rilpivirine, and tenofovir disoproxil fumarate).

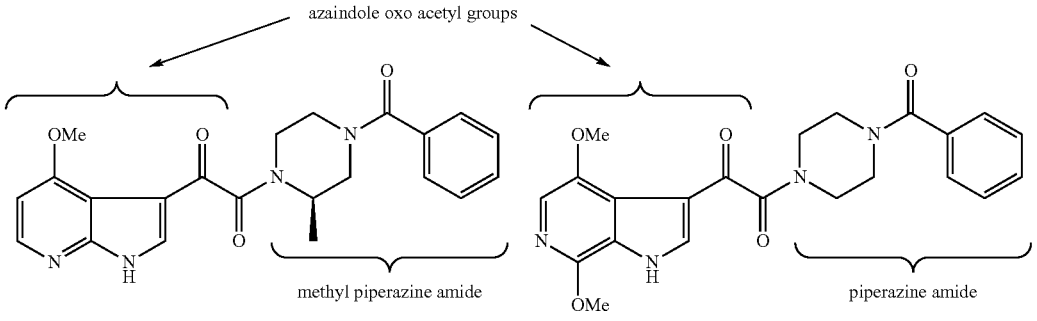
Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g., most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

HIV attachment inhibitors are a novel subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. A disclosure describing indoles of which the structure shown below for BMS-705 is representative, has been disclosed (Antiviral Indoleoxoacetyl Piperazine Derivatives).

BMS-705



Two other compounds, referred to in the literature as BMS-806 and BMS-043 have been described in both the academic and patent art:



BMS-806 BMS-043

Some description of their properties in human clinical trials has been disclosed in the literature.

It should be noted that in all three of these structures, a piperazine amide (in these three structures a piperazine phenyl amide) is present and this group is directly attached to an oxoacetyl moiety. The oxoacetyl group is attached at the 3-position of 4-fluoro indole in BMS-705 and to the 3 position of substituted azaindoles in BMS-806 and BMS-043.

In an effort to obtain improved anti-HIV compounds, later publications described in part, modified substitution patterns on the indoles and azaindoles. Examples of such efforts include: (1) novel substituted indoleoxoacetic piperazine derivatives, (2) substituted piperazinyloxoacetylindole derivatives, and (3) substituted azaindoleoxoacetic piperazine derivatives.

Replacement of these groups with other heteroaromatics or substituted heteroaromatics or bicyclic hydrocarbons was also shown to be feasible. Examples include: (1) indole, azaindole and related heterocyclic amidopiperazine derivatives; (2) bicyclo[4.4.0] antiviral derivatives; and (3) diazaindole derivatives.

A select few replacements for the piperazine amide portion of the molecules have also been described in the art and among these examples are (1) some piperidine alkenes; (2) some pyrrolidine amides; (3) some N-aryl or heteroaryl piperazines; (4) some piperazinyl ureas; and (5) some carboline-containing compounds.

Method(s) for preparing prodrugs for this class of compounds are disclosed in Prodrugs of Piperazine and Substituted Piperidine Antiviral Agents (Ueda et al., U.S. Publication No. 2005/0209246 or WO 2005/090367 A1).

A published PCT patent application WO 2003/103607 A1 (Jun. 11, 2003) discloses an assay useful for assaying some HIV inhibitors.

Several published patent applications describe combination studies with piperazine benzamide inhibitors, for example, U.S. Publication No. 2005/0215543 (WO 2005/102328 A1), U.S. Publication No. 2005/0215544 (WO 2005/102391 A1), and U.S. Publication No. 2005/0215545 (WO 2005/102392 A2).

A publication on new compounds in this class of attachment inhibitors (Wang, J. et al., *Org. Biol. Chem.,* 3:1781-1786 (2005)) and a patent application on some more remotely related compounds have appeared WO 2005/016344 published on Feb. 24, 2005.

Published patent applications WO 2005/016344 and WO 2005/121094 also describe piperazine derivatives which are HIV inhibitors. Other references in the HIV attachment area include U.S. Publication Nos. 2007/0155702, 2007/0078141 and 2007/0287712, WO 2007/103456, as well as U.S. Pat. Nos. 7,348,337 and 7,354,924. A literature reference is *J. Med. Chem.,* 50:6535 (2007).

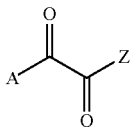
What is therefore needed in the art are new HIV attachment inhibitor compounds, and compositions thereof, which are efficacious against HIV infection.

Of particular interest are new cyclic hydrazine derivatives as HIV attachment inhibitor compounds, described herein. The compounds of the present invention are cyclic hydrazine derivatives, which are believed to be structurally distinct from the piperazine aryl amide HIV attachment inhibitors set forth in the existing literature.

SUMMARY OF THE INVENTION

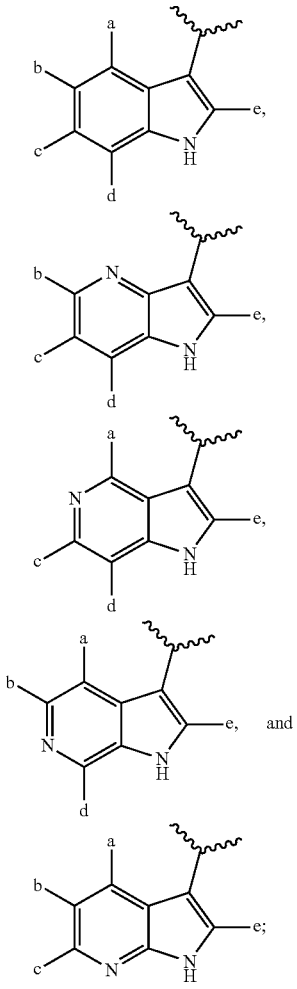
The present invention provides compounds of Formula I below, the pharmaceutically acceptable salts and/or solvates (e.g., hydrates) thereof, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, their pharmaceutically acceptable salts and/or solvates are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

One embodiment of the present invention is directed to a compound of Formula I, including pharmaceutically acceptable salts thereof:



I

wherein A is selected from the group consisting of:



wherein

a, b, c, d and e are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^{56}$, XR^{57}, NA^1A^2, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, Q, and E;

B is selected from the group consisting of —$C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, aryl, heteroaryl, heteroalicyclic, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $C(O)R^7$, XR^{8a}, (C_{1-6})alkyl$NR^{40}R^{41}$, (C_{1-6})alkyl$COOR^{8b}$; wherein said aryl, heteroaryl, and heteroali-

cyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is napthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

Q is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of $C(O)NR^{55}R^{56}$, hydroxy, cyano and XR^{57};

E is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, —$C(O)NR^{56}R^{57}$, $C(O)R^{57}$, $SO_2(C_{1-6})$alkyl and SO_2Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, (C_{1-6})thioalkoxy, cyano, halogen, nitro, —$C(O)R^{57}$, benzyl, —$NR^{42}C(O)$—(C_{1-6})alkyl, —$NR^{42}C(O)$—(C_{3-6})cycloalkyl, —$NR^{42}C(O)$-aryl, —$NR^{42}C(O)$-heteroaryl, —$NR^{42}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{42}S(O)_2$—(C_{1-6})alkyl, —$NR^{42}S(O)_2$—(C_{3-6})cycloalkyl, —$NR^{42}S(O)_2$-aryl, —$NR^{42}S(O)_2$-heteroaryl, —$NR^{42}S(O)$2-heteroalicyclic, $S(O)_2(C_{1-6})$alkyl, $S(O)_2$aryl, —$S(O)_2NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6})alkyl$C(O)NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alkyl$NR^{42}R^{43}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, cyano, halogen, nitro, —$C(O)R^{57}$, benzyl, —$NR^{48}C(O)$—(C_{1-6})alkyl, —$NR^{48}C(O)$—(C_{3-6})cycloalkyl, —$NR^{48}C(O)$-aryl, —$NR^{48}C(O)$-heteroaryl, —$NR^{48}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{48}S(O)_2$—(C_{1-6})alkyl, —$NR^{48}S(O)_2$—(C_{3-6})cycloalkyl, —$NR^{48}S(O)_2$-aryl, —$NR^{48}S(O)_2$-heteroaryl, —$NR^{48}S(O)_2$-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$, $NHC(O)NR^{48}R^{49}$, $OC(O)NR^{48}R^{49}$, $NHC(O)OR^{54'}$, (C_{1-6})alkyl$NR^{48}R^{49}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^7 is selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R^7, R^8, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^8 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F or (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

X is selected from the group consisting of NH or NCH_3, O, and S;

R^{40} and R^{41} are independently selected from the group consisting of (a) hydrogen; (b) (C_{1-6})alkyl or (C_{3-7})cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F or different functional groups: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; and (c) (C_{1-6})alkoxy, aryl, heteroaryl or heteroalicyclic; or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents

selected from the group F; wherein for R^{40} and R^{41} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is $C(O)NR^{40}R^{41}$, at least one of R^{40} and R^{41} is not selected from groups (a) or (b);

R^{42} and R^{43} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, allyl, (C_{1-6})alkoxy, (C_{3-7}) cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G or different functional groups: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; wherein for R^{42} and R^{43} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^{46} is selected from the group consisting of H, phenyl, aryl, heteroaryl and (C_{1-6})alkyl, OR^{57}, and $NR^{55}R^{56}$;

R^{47} is selected from the group consisting of H, amino, hydroxyl, phenyl, aryl, heteroaryl and (C_{1-6})alkyl;

R^{48} and R^{49} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, phenyl, aryl and heteroaryl;

R^{50} is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, and benzyl; wherein each of said (C_{1-6}) alkyl, (C_{3-7})cycloalkyl and benzyl are optionally substituted with one to three same or different (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl

R^{54} is selected from the group consisting of hydrogen and (C_{1-6})alkyl;

$R^{54'}$ is (C_{1-6})alkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; and

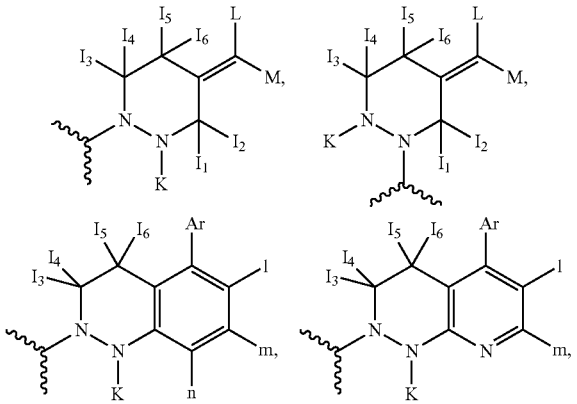
R^{57} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, aryl, heteroaryl; and

A^1 and A^2 are independently selected from hydrogen, (C_{1-6}) alkyl, aryl, heteroaryl, $SO2D^1$, $SO2ND^2D^3$, COD^4, $COCOD^4$, $COOD^4$, $COND^5D^6$, $COCOND^5D^6$, $COCOOD^4$, $C(=ND^7)D^8$, $C(=ND^9)ND^{10}D^{11}$;

A^1 and A^2 can either never connect with each other, or conjoin to form a ring structure;

D^1, D^2, D^3, D^4, D^5, D^6, D^7, D^8, D^9, D^{10}, and D^{11} are each independently selected from the group consisting of H, C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_{20} alkenyl or the carbon-carbon triple bond of said C_3-C_{20} alkynyl are not the point of attachment to the nitrogen to which D^2, D^3, D^5, D^6, D^7, D^9, D^{10}, and D^{11} is attached; wherein said C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, aryl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether is optionally substituted with one to three same or different of the following functionalities: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide and steroid, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

Z is selected from the group consisting of:



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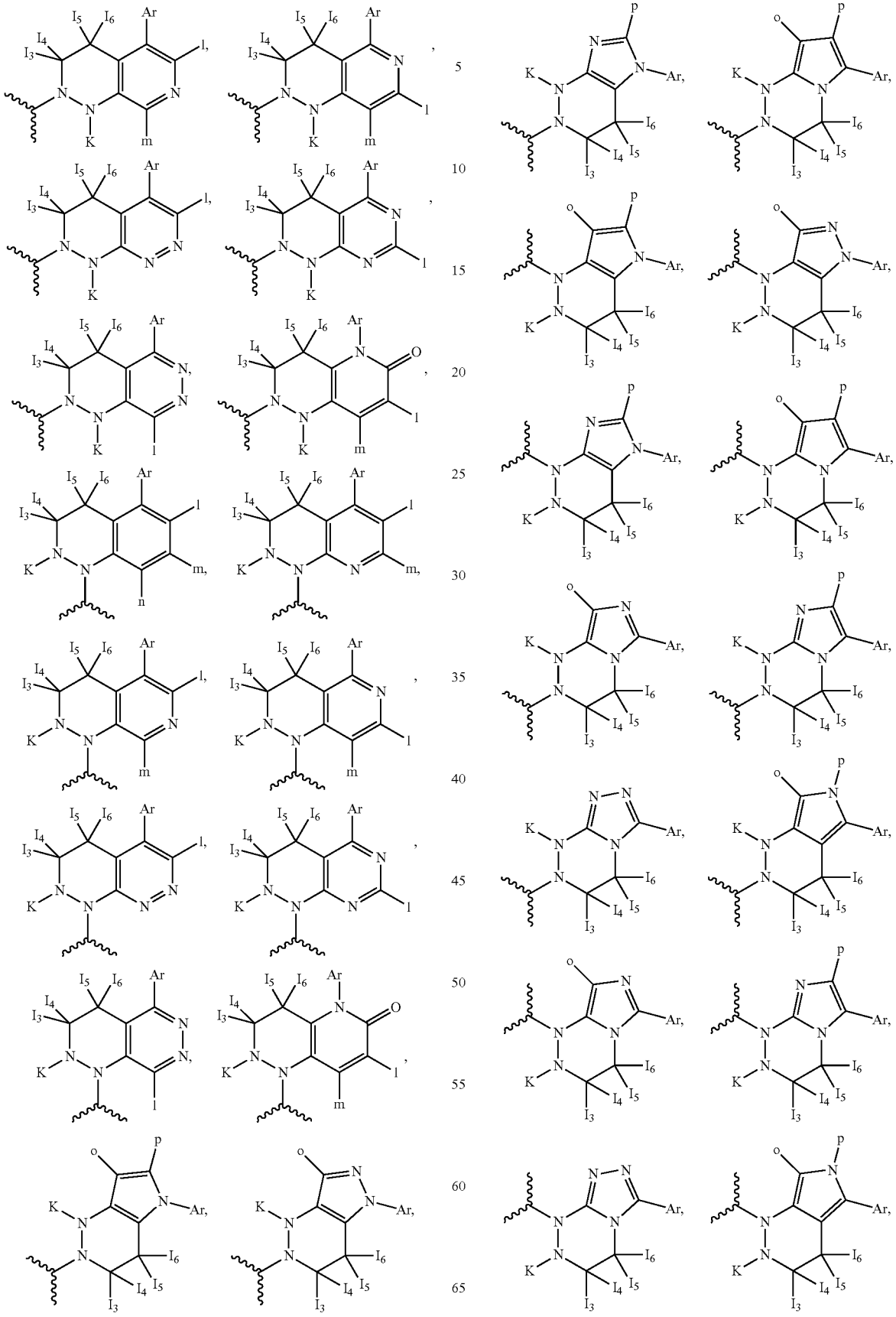

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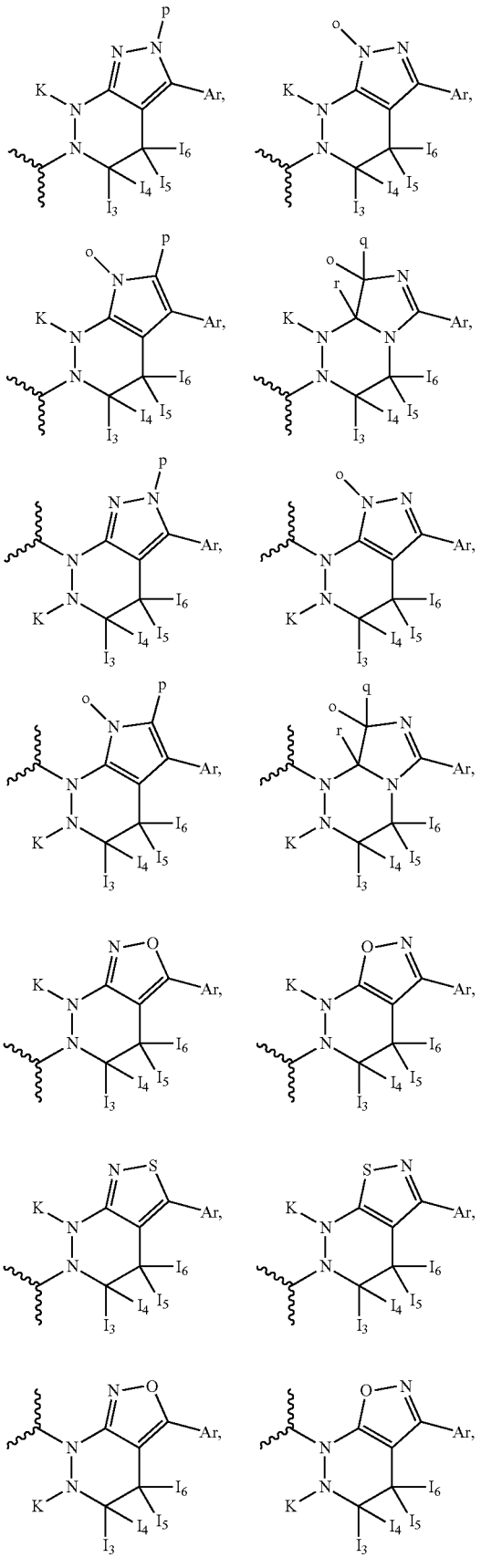

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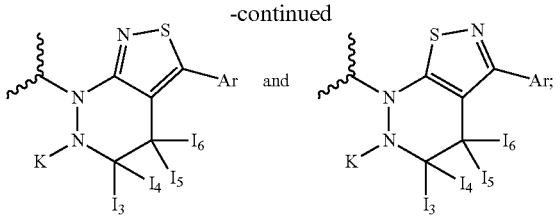


K is selected from the group consisting of hydrogen, hydroxyl, $OR^{54'}$, (C_{1-6})alkyl and (C_{3-7})cycloalkyl;

I_1, I_2, I_3, I_4, I_5, and I_6 are each independently selected from the group consisting of H, halogen, (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl, $CR_{81}R_{82}OR_{83}$, COR_{84}, $COOR_{85}$, or $CONR_{86}R_{87}$; wherein each of said alkyl and cycloalkyl being optionally substituted with one to three same or different cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R_{81}, R_{82}, R_{83}, R_{84}, R_{85}, R_{86}, and R_{87} are each independently selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl;

L is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{1-6})alkynyl, (C_{3-6}) cycloalkyl, halogen, cyano, $CONR^{40}R^{41}$, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $C(O)R^8$, $COOR^8$ tetrahydrofuryl, pyrrolidinyl, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, (C_{1-6})alkynyl, phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group G; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

M is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group W; and heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

W is selected from the group consisting of (C_{1-3})alkyl, hydroxy, (C_{1-3})alkoxy, halogen and $—NR^{42}R^{43}$; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogens;

l, m and n are selected from the group consisting of H, halogen, OR^8, CN, $(C_1$-$C_4)$ alkyl, $(C_3$-$C_6)$ cycloalkyl group and Group C; alkyl and $(C_3$-$C_6)$ cycloalkyl group optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$;

o and p are selected from the group consisting of H, OH, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, halogen (attached to carbon only), and Group C;

q and r are selected from the group consisting of H, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$ and Group C;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

Group C is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

Group D is selected from the group consisting of OH, OR^8, NA^1A^2, CN, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$;

Another embodiment of the present invention is directed to a method for treating mammals infected with a virus, especially wherein the virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I above, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formula I can be administered in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

Another embodiment of the present invention is a pharmaceutical composition comprising an antiviral effective amount of a compound of Formula I and one or more pharmaceutically acceptable carriers, excipients, diluents and optionally in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

In another embodiment of the invention there is provided one or more methods for making the compounds of Formula I.

The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Since the compounds of the present invention may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

Definitions

Unless otherwise specifically set forth elsewhere in the application, one or more of the following terms may be used herein, and shall have the following meanings:

The term "H" refers to hydrogen, including its isotopes.

The term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

"C_1-C_4 fluoroalkyl" refers to F-substituted C_1-C_4 alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F atom.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $—NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl, diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $—NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass

systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and —NR^xR^y, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and —NR^xR^y with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an —OH group.

An "alkoxy" group refers to both an —O-alkyl and an —O-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an —O-aryl and an —O-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O— group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O— group with heteroalicyclic as defined herein.

A "thiohydroxy" group refers to an —SH group.

A "thioalkoxy" group refers to both an S-alkyl and an —S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an —S-aryl and an —S-heteroaryl group, as defined herein.

A "thioheteroaryloxy" group refers to a heteroaryl-S— group with heteroaryl as defined herein.

A "thioheteroalicycloxy" group refers to a heteroalicyclic-S— group with heteroalicyclic as defined herein.

A "carbonyl" group refers to a —C(=O)—R" group, where R" is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An "aldehyde" group refers to a carbonyl group where R" is hydrogen.

A "thiocarbonyl" group refers to a —C(=S)—R" group, with R" as defined herein.

A "Keto" group refers to a —CC(=O)C— group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$— group with said Z being a halogen.

A "C-carboxy" group refers to a —C(=O)O—R" groups, with R" as defined herein.

An "O-carboxy" group refers to a R"C(—O)O-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is hydrogen.

A "trihalomethyl" group refers to a —CZ_3, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$— groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$— group with Z as defined above and R^x being H or (C_{1-6})alkyl.

A "sulfinyl" group refers to a —S(=O)—R" group, with R" being (C_{1-6})alkyl.

A "sulfonyl" group refers to a —$S(=O)_2R$" group with R" being (C_{1-6})alkyl.

A "S-sulfonamido" group refers to a —$S(=O)_2NR^XR^Y$, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-Sulfonamido" group refers to a R"$S(=O)_2NR_X$— group, with R_x being H or (C_{1-6})alkyl.

A "O-carbamyl" group refers to a —$OC(=O)NR^XR^Y$ group, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "O-thiocarbamyl" group refers to a —$OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$— group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "amino" group refers to an —NH_2 group.

A "C-amido" group refers to a —$C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "C-thioamido" group refers to a —$C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-amido" group refers to a $R^xC(=O)NR^y$— group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "ureido" group refers to a —$NR^x(=O)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "guanidino" group refers to a —$R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6}) alkyl.

A "guanyl" group refers to a $R^xR^yNC(=N)$— group, with R^x and R^y independently being H or (C_{1-6})alkyl.

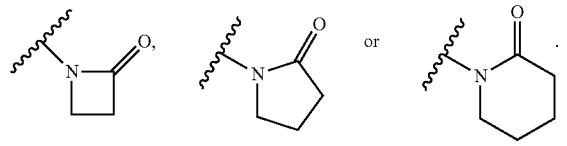
A "cyano" group refers to a —CN group.

A "silyl" group refers to a —$Si(R")_3$, with R" being (C_{1-6}) alkyl or phenyl.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6})alkyl.

A "hydrazino" group refers to a —$NR^xNR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "4, 5, or 6 membered ring cyclic N-lactam" group refers to



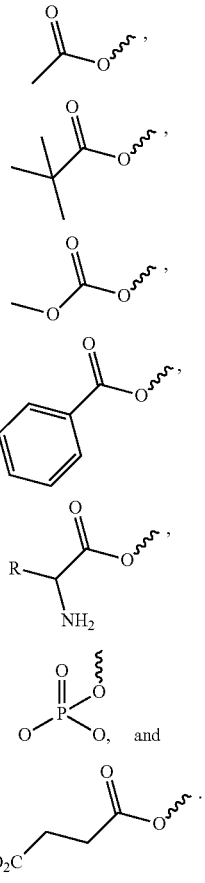
Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

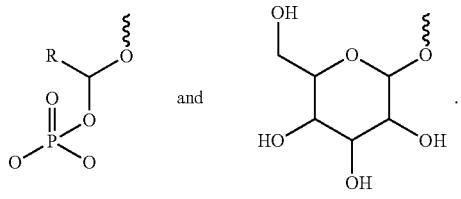
Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this disclosure. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfuric acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g., hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris (hydroxymethyl)-aminomethane), or with bases such as piperidine or morpholine.

As stated above, the compounds of the invention also include "prodrugs". The term "prodrug" as used herein encompasses both the term "prodrug esters" and the term "prodrug ethers". The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

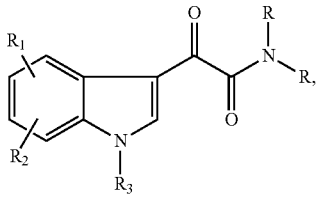
Examples of such prodrug esters include

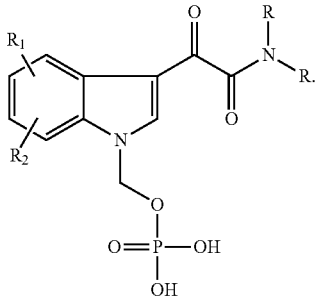


The term "prodrug ethers" include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include

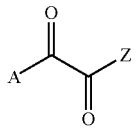


Prodrug derivatives in which the prodrug moiety is attached to the indole N atom are also considered part of this invention. These prodrugs can be prepared by substitution of the indole N with a moiety that modifies the physical properties of the compound and can be unmasked either by chemical or enzymatic degradation. Examples of R_3 include acyl derivatives similar to those described above. A preferred prodrug is the phosphonoxymethyl moiety which can be introduced using methods previously described and converted to pharmaceutically acceptable salt forms that confer chemical stability and advantageous physical properties:



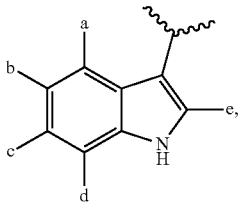


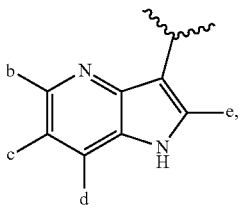
As set forth above, the invention is directed to compounds of Formula I, including pharmaceutically acceptable salts thereof:

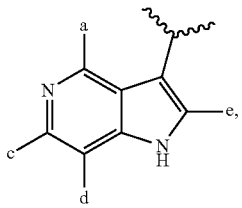


I

wherein A is selected from the group consisting of:







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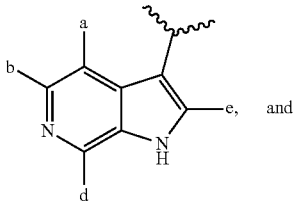
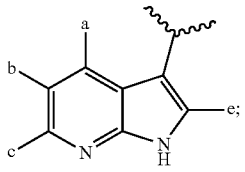


and



wherein

a, b, c, d and e are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^{56}$, XR^{57}, NA^1A^2, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, Q, and E;

B is selected from the group consisting of —$C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, aryl, heteroaryl, heteroalicyclic, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $C(O)R^7$, XR^{8a}, (C_{1-6})alkyl$NR^{40}R^{41}$, (C_{1-6})alkyl$COOR^{8b}$; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is napthyl or substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

Q is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7}) cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of $C(O)NR^{55}R^{56}$, hydroxy, cyano and XR^{57};

E is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7}) cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6})alkyl and (C_{2-6})alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, —$C(O)NR^{56}R^{57}$, $C(O)R^{57}$, $SO_2(C_{1-6})$alkyl and SO_2Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7}) cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6}) alkoxy, aryloxy, (C_{1-6})thioalkoxy, cyano, halogen, nitro, —$C(O)R^{57}$, benzyl, —$NR^{42}C(O)$—(C_{1-6})alkyl, —$NR^{42}C(O)$—(C_{3-6})cycloalkyl, —$NR^{42}C(O)$-aryl, —$NR^{42}C(O)$-heteroaryl, —$NR^{42}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{42}S(O)_2$—(C_{1-6})alkyl, —$NR^{42}S(O)_2$—(C_{3-6})cycloalkyl, —$NR^{42}S(O)_2$-aryl, —$NR^{42}S(O)_2$-heteroaryl, —$NR^{42}S(O)_2$-heteroalicyclic, $S(O)_2(C_{1-6})$alkyl, $S(O)_2$aryl, —S(O)2 $NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6})alkyl$C(O)NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alkyl$NR^{42}R^{43}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7

ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, cyano, halogen, nitro, —C(O)R^{57}, benzyl, —NR^{48}C(O)—(C_{1-6})alkyl, —NR^{48}C(O)—(C_{3-6})cycloalkyl, —NR^{48}C(O)-aryl, —NR^{48}C(O)-heteroaryl, —NR^{48}C(O)-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{48}S(O)_2$—(C_{1-6})alkyl, —$NR^{48}S(O)_2$—(C_{3-6})cycloalkyl, —NR^{48}S(O)2-aryl, —$NR^{48}S(O)_2$-heteroaryl, —NR^{48}S(O)2-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, $NR^{48}R^{49}$, (C_{1-6})alkyl C(O)$NR^{48}R^{49}$, C(O)$NR^{48}R^{49}$, NHC(O)$NR^{48}R^{49}$, OC(O)$NR^{48}R^{49}$, NHC(O)$OR^{54'}$, (C_{1-6})alkyl$NR^{48}R^{49}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^7 is selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R^7, R^8, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^8 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F or (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic; wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

X is selected from the group consisting of NH or NCH_3, O, and S;

R^{40} and R^{41} are independently selected from the group consisting of (a) hydrogen; (b) (C_{1-6})alkyl or (C_{3-7})cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F or different functional groups: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; and (c) (C_{1-6})alkoxy, aryl, heteroaryl or heteroalicyclic; or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; wherein for R^{40} and R^{41} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is C(O)$NR^{40}R^{41}$, at least one of R^{40} and R^{41} is not selected from groups (a) or (b);

R^{42} and R^{43} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, allyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G or different functional groups: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; wherein for R^{42} and R^{43} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from

the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^{46} is selected from the group consisting of H, phenyl, aryl, heteroaryl and (C_{1-6})alkyl, OR^{57}, and $NR^{55}R^{56}$;

R^{47} is selected from the group consisting of H, amino, hydroxyl, phenyl, aryl, heteroaryl and (C_{1-6})alkyl;

R^{48} and R^{49} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, phenyl, aryl and heteroaryl;

R^{50} is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, and benzyl; wherein each of said (C_{1-6}) alkyl, (C_{3-7})cycloalkyl and benzyl are optionally substituted with one to three same or different (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl

R^{54} is selected from the group consisting of hydrogen and (C_{1-6})alkyl;

$R^{54'}$ is (C_{1-6})alkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; and

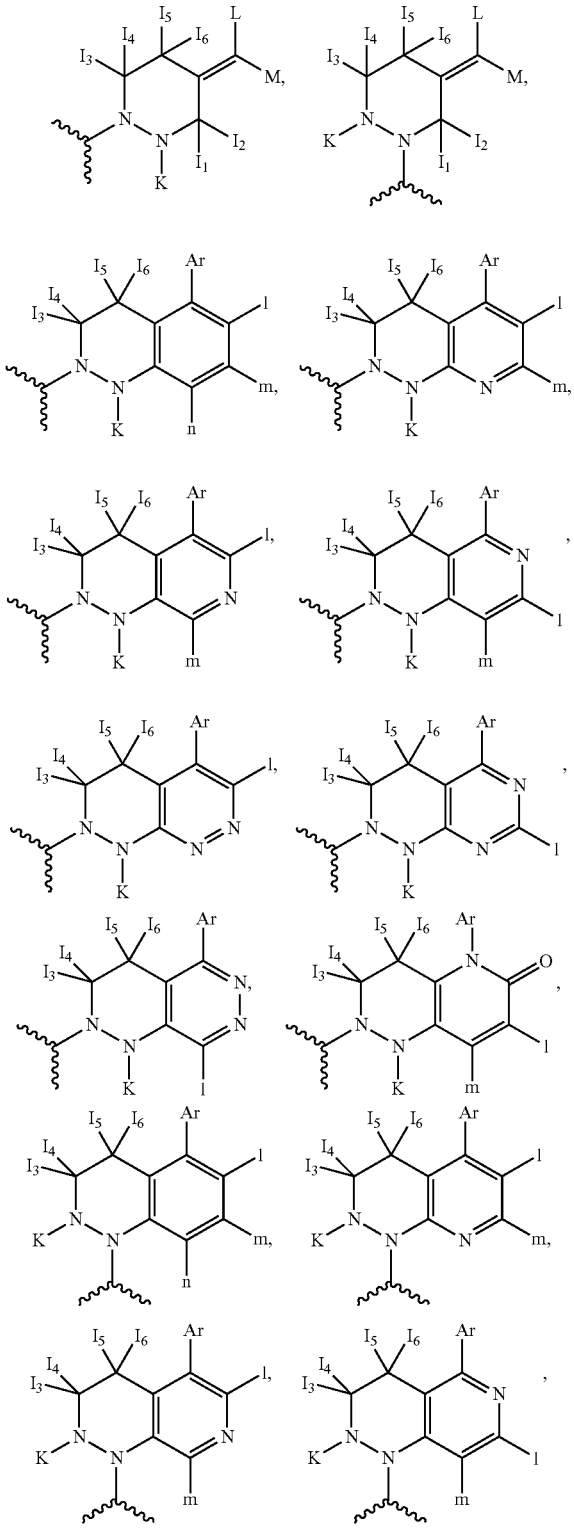
R^{57} is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, aryl, heteroaryl; and

A^1 and A^2 are independently selected from hydrogen, (C_{1-6}) alkyl, aryl, heteroaryl, $SO2D^1$, $SO2ND^2D^3$, COD^4, $COCOD^4$, $COOD^4$, $COND^5D^6$, $COCOND^5D^6$, $COCOOD^4$, $C(=ND^7)D^8$, $C(=ND^9)ND^{10}D^{11}$;

A^1 and A^2 can either never connect with each other, or conjoin to form a ring structure;

D^1, D^2, D^3, D^4, D^5, D^6, D^7, D^8, D^9, D^{10}, and D^{11} are each independently selected from the group consisting of H, C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo [4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_{20} alkenyl or the carbon-carbon triple bond of said C_3-C_{20} alkynyl are not the point of attachment to the nitrogen to which D^2, D^3, D^5, D^6, D^7, D^9, D^{10}, and D^{11} is attached; wherein said C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, aryl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether is optionally substituted with one to three same or different of the following functionalities: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide and steroid, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

Z is selected from the group consisting of:



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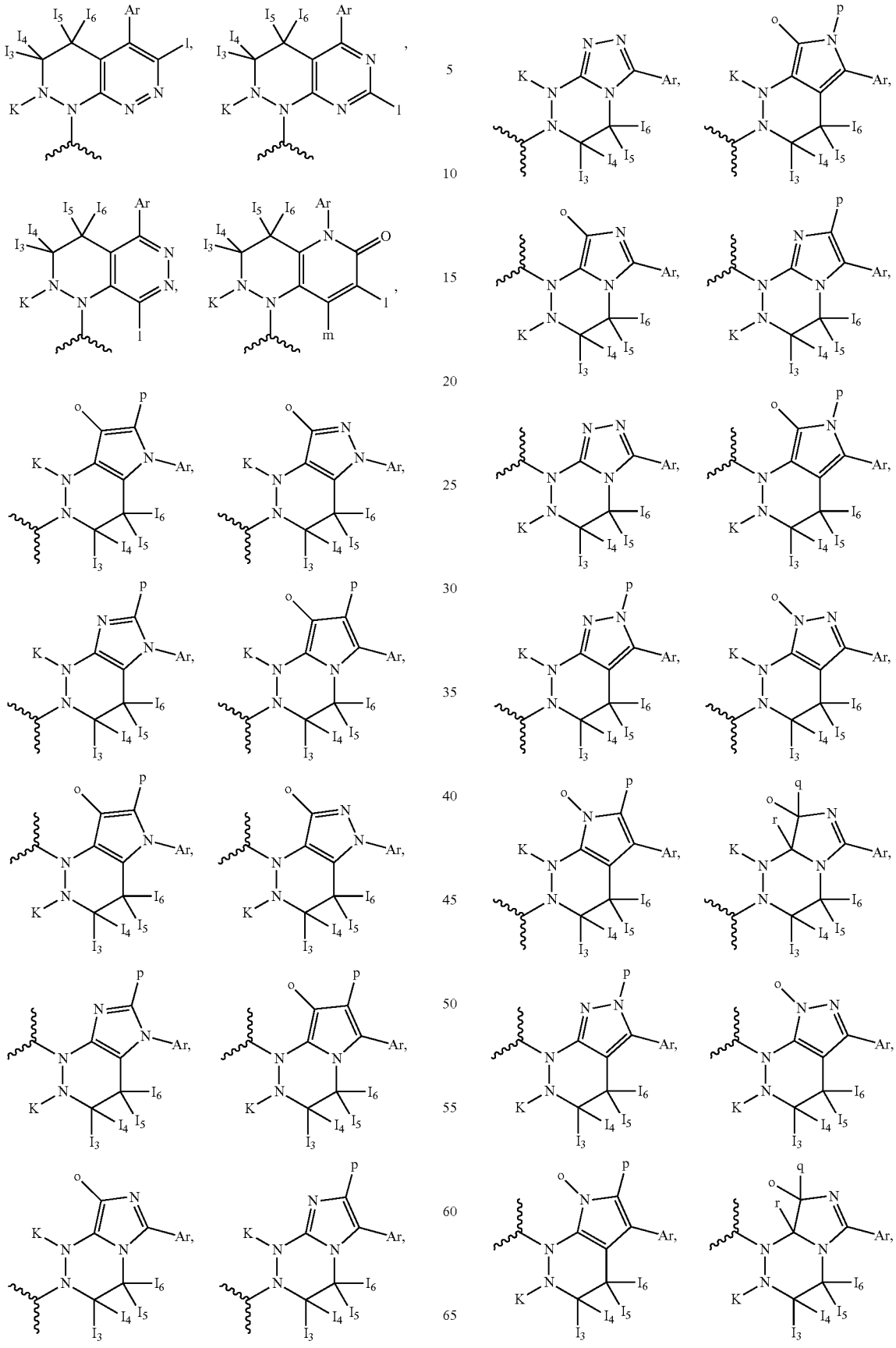

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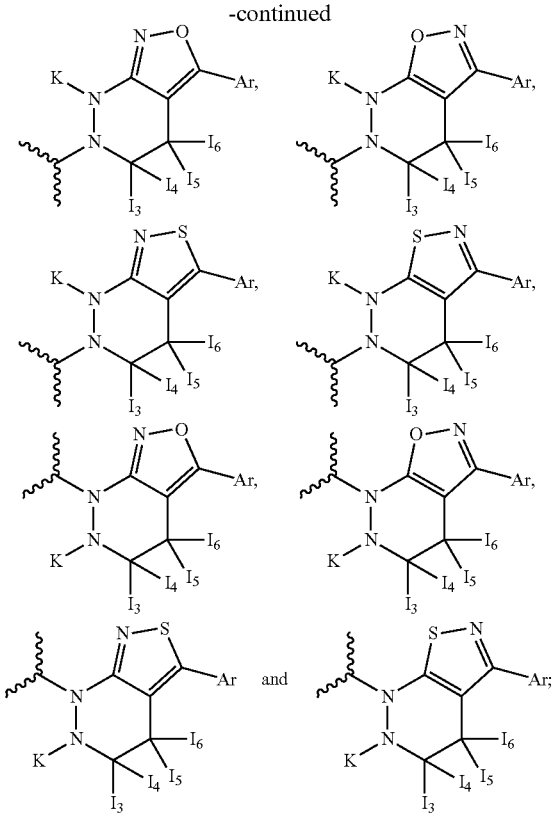


K is selected from the group consisting of hydrogen, hydroxyl, $OR^{54'}$, (C_{1-6})alkyl and (C_{3-7})cycloalkyl;

I_1, I_2, I_3, I_4, I_5, and I_6 are each independently selected from the group consisting of H, halogen, (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl, $CR_{81}R_{82}OR_{83}$, COR_{84}, $COOR_{85}$, or $CONR_{86}R_{87}$; wherein each of said alkyl and cycloalkyl being optionally substituted with one to three same or different cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R_{81}, R_{82}, R_{83}, R_{84}, R_{85}, R_{86}, and R_{87} are each independently selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl;

L is selected from the group consisting of hydrogen, (C_{1-6}) alkyl, (C_{1-6})alkynyl, (C_{3-6}) cycloalkyl, halogen, cyano, $CONR^{40}R^{41}$, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $COOR^8$, $C(O)R^8$, $COOR^8$, tetrahydrofuryl, pyrrolidinyl, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, (C_{1-6})alkynyl, phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group G; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

M is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group W; and heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

W is selected from the group consisting of (C_{1-3})alkyl, hydroxy, (C_{1-3})alkoxy, halogen and $—NR^{42}R^{43}$; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogens;

l, m and n are selected from the group consisting of H, halogen, OR^8, CN, $(C_1$-$C_4)$ alkyl, $(C_3$-$C_6)$ cycloalkyl group and Group C; alkyl and $(C_3$-$C_6)$ cycloalkyl group optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CON\,A^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$;

o and p are selected from the group consisting of H, OH, $(C_1$-$C_4)$ alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CON\,A^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$, $(C_3$-$C_6)$ cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CON\,A^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$, halogen (attached to carbon only), and Group C;

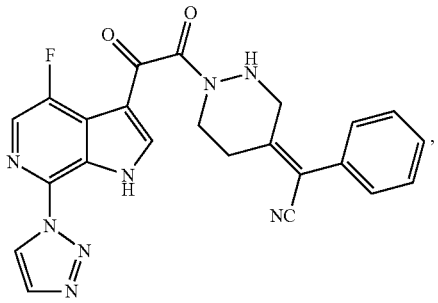
q and r are selected from the group consisting of H, $(C_1$-$C_4)$ alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CON\,A^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$, $(C_3$-$C_6)$ cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CON\,A^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$ and Group C;

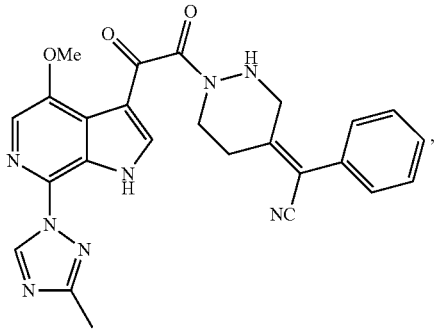
Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

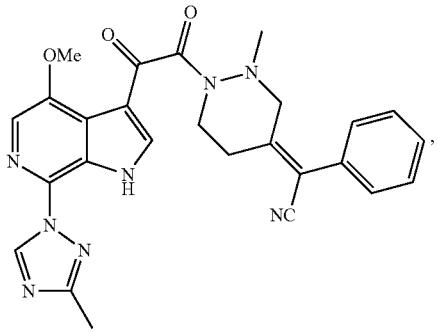
Group C is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

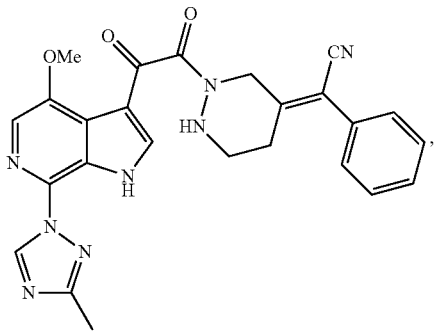
Group D is selected from the group consisting of OH, OR^8, NA^1A^2, CN, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$, $(C_1$-$C_4)$ alkyl, $(C_3$-$C_6)$ cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2N\,A^1A^2$;

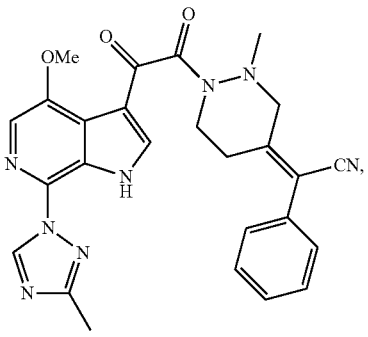
More preferred compounds of Formula I include those which are selected from the group consisting of:











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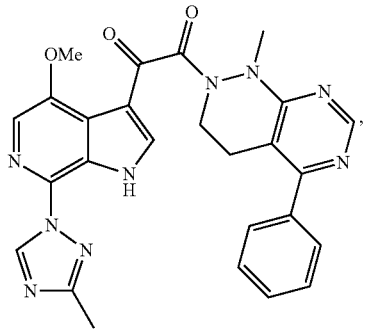

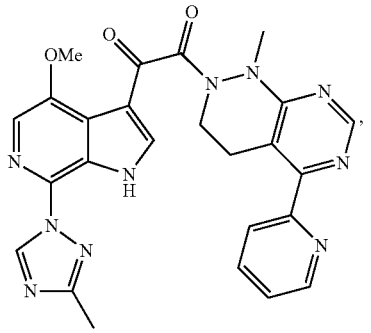

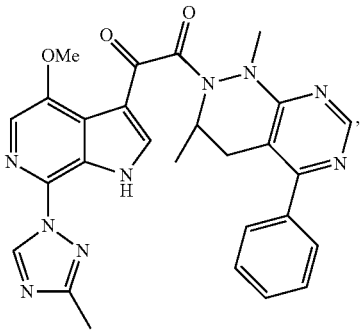

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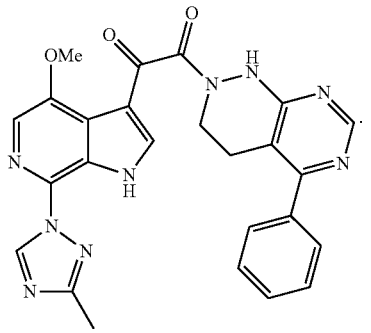
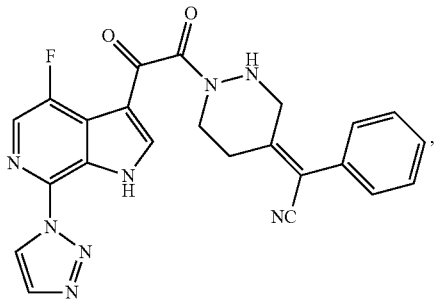


Of the foregoing,



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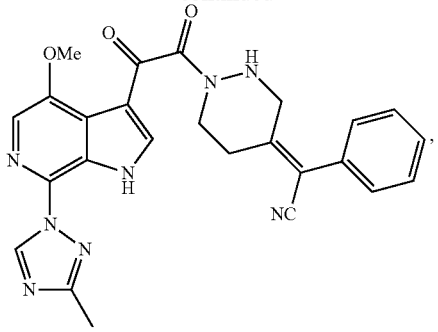

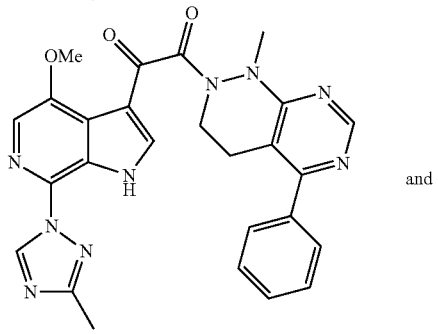

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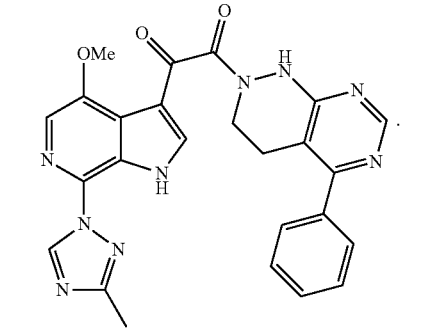


are even more preferred.

The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and diluents available to the skilled artisan. One or more adjuvants may also be included.

Thus, in accordance with the present disclosure, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of one or more of the compounds of Formula I, together with one or more pharmaceutically acceptable carriers, excipients or diluents. As used herein, the term "antiviral effective amount" means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, i.e., inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing, ameliorating or healing diseases associated with HIV infection.

The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this disclosure can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Also contemplated herein are combinations of the compounds of Formula I herein set forth, together with one or more agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

Drug Name	Manufacturer	Indication
Rilpivirine	Tibotec	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)

-continued

Drug Name	Manufacturer	Indication
Complera ®	Gilead	HIV infection, AIDS, ARC; combination with emtricitabine, rilpivirine, and tenofovir disoproxil fumarate
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex	Sight threatening CMV peripheral CMV retinitis
Darunavir	Tibotec-J & J	HIV infection, AIDS, ARC (protease inhibitor)
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)

-continued

Drug Name	Manufacturer	Indication
Efavirenz (DMP 266, Sustiva ®) (−)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methy1-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Etravirine	Tibotec/J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)

-continued

Drug Name	Manufacturer	Indication
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV Infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread ®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
Emtriva ® (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
Combivir ®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Abacavir succinate (or Ziagen ®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Reyataz ® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
Fuzeon ® (Enfuvirtide or T-20)	Roche/Trimeris	HIV infection AIDs, viral Fusion inhibitor
Lexiva ® (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDs, viral protease inhibitor
Selzentry Maraviroc; (UK 427857)	Pfizer	HIV infection AIDs, (CCR5 antagonist, in development)
Trizivir ®	GSK	HIV infection AIDs, (three drug combination)
Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDs, (CCR5 antagonist, in development)
TAK-652	Takeda	HIV infection AIDs, (CCR5 antagonist, in development)
GSK 873140 (ONO-4128)	GSK/ONO	HIV infection AIDs, (CCR5 antagonist, in development)
Integrase Inhibitor MK-0518 Raltegravir	Merck	HIV infection AIDs
Truvada ®	Gilead	Combination of Tenofovir disoproxil fumarate salt (Viread ®) and Emtriva ® (Emtricitabine)
Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead/Japan Tobacco	HIV Infection AIDs in development
Triple drug combination Atripla ®	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (Viread ®), Emtriva ® (Emtricitabine), and Sustiva ® (Efavirenz)
Festinavir ®	Oncolys BioPharma	HIV infection AIDs in development
CMX-157 Lipid conjugate of nucleotide tenofovir	Chimerix	HIV infection AIDs
GSK1349572 Integrase inhibitor	GSK	HIV infection AIDs

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	Wyeth Lederle Labs	AIDS, Kaposi's sarcoma
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the disclosure herein set forth may be used in combination with other HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in *Drugs of the Future,* 24(12):1355-1362 (1999); *Cell,* 9:243-246 (Oct. 29, 1999); and *Drug Discovery Today,* 5(5):183-194 (May 2000) and Meanwell, N.A. et al., "Inhibitors of the entry of HIV into host cells", *Curr. Op. Drug Disc. Dev,* 6(4):451-461 (2003). Specifically the compounds can be utilized in combination with other attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor.

It will be understood that the scope of combinations of the compounds of this disclosure with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is REYATAZ® (active ingredient Atazanavir). Typically a dose of 300 to 600 mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500 mgs). Another preferred inhibitor of HIV protease is KALETRA®. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)—N-(t-butylcarboxa-

mido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. Pat. No. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine. (The preparation of ddC, ddI and AZT are also described in EP 0 484 071.)

In such combinations the compound of the present disclosure and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

METHODS OF SYNTHESIS

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof. The compounds may be made by methods known in the art including those described after the Abbreviations and including variations within the skill of the art. Some reagents and intermediates are known in the art. Other reagents and intermediates can be made by methods known in the art using readily available materials. The variables (e.g. numbered "R" substituents) used to describe the synthesis of the compounds are intended only to illustrate how to make the compounds and are not to be confused with variables used in the claims or in other sections of the specification. The following methods are for illustrative purposes and are not intended to limit the scope of the invention.

ABBREVIATIONS

One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

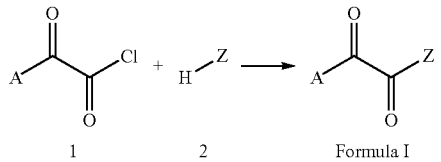
h=hour(s)
rt=room temperature
mol=mole(s)
mmol=millimole(s)
g=gram(s)
mg=milligram(s)
mL=milliliter(s)
TFA=trifluoroacetic Acid
DCE=1,2-Dichloroethane
CH_2Cl_2=dichloromethane
TPAP=tetrapropylammonium perruthenate
THF=tetrahydrofuran
DEPBT=3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DMAP=4-dimethylaminopyridine
P-EDC=polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDC=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
DMF=N,N-dimethylformamide
Hunig's Base=N,N-diisopropylethylamine
MCPBA=meta-chloroperbenzoic acid
azaindole=1H-pyrrolo-pyridine
4-azaindole=1H-pyrrolo[3,2-b]pyridine
5-azaindole=1H-pyrrolo[3,2-c]pyridine
6-azaindole=1H-pyrrolo[2,3-c]pyridine
7-azaindole=1H-pyrrolo[2,3-b]pyridine
PMB=4-methoxybenzyl
DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone
OTf=trifluoromethanesulfonoxy
NMM=4-methylmorpholine
PIP-COPh=1-benzoylpiperazine
NaHMDS=sodium hexamethyldisilazide
EDAC=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
TMS=trimethylsilyl
DCM=dichloromethane
DCE=dichloroethane
MeOH=methanol
THF=tetrahydrofuran
EtOAc=ethyl acetate
LDA=lithium diisopropylamide
TMP-Li=2,2,6,6-tetramethylpiperidinyl lithium
DME=dimethoxyethane
DIBALH=diisobutylaluminum hydride
HOBT=1-hydroxybenzotriazole
CBZ=benzyloxycarbonyl
PCC=pyridinium chlorochromate
TBTU=O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
DEBPT=3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
BOP=benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate

Preparation of Compounds of Formula I

Preparation of template A-CO—CO—Cl and A-CO—CO—OH has been described in detail in WO-00076521, WO-0162255, WO-0204440, WO-02062423, WO-02085301, WO-03068221 and US-2004/0063744.

Standard conditions such as reacting amine with acyl halide 1 (Scheme 1a) and carboxyl acid 3 (Scheme 1b) can be used to prepare the desired amide products. Some general references of these methodologies and directions for use are contained in "Comprehensive Organic Transformation" by Richard C. Larock, Wiley-VCH, New York, 1989, 972 (Carboxylic acids to amides), 979 (Acid halides to amides).

Scheme 1a

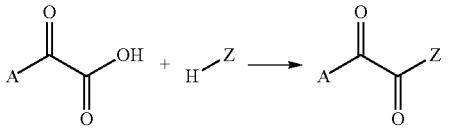


1 2 Formula I

Scheme 1a depicts a general method for forming an amide from cyclic hydrazine derivative 2 and acyl chloride 1. An appropriate base (from catalytic to an excess amount) selected from sodium hydride, potassium carbonate, triethylamine, DBU, pyridine, DMAP or di-isopropyl ethyl amine was added into a solution of cyclic hydrazine 2 and acyl chloride 1 in an appropriate solvent selected from dichloromethane, chloroform, benzene, toluene, THF, diethyl ether, dioxane, acetone, N,N-dimethylformamide or pyridine at room temperature. Then reaction was carried out at either

room temperature or evaluated temperature up to 150° C. over a period of time (30 minutes to 48 hours) to afford the structure of Formula I. Some selected references involving such reactions include a) *Indian J. Chem., Sect B* 1990, 29, 1077; 2) *Chem. Sci.* 1998, 53, 1216; 3) *Chem. Pharm. Bull.* 1992, 40, 1481; 4) *Chem. Heterocycl. Compd.* 2002, 38, 539.

Scheme 1b



3 2 Formula I

Alternatively, as shown in Scheme 1b, a cyclic hydrazine 2 can be coupled with an acid 3 using standard amide bond or peptide bond forming coupling reagents. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products. The combination of EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform have been utilized most frequently but DEPBT, or other coupling reagents such as PyBop could be utilized. Another useful coupling condition employs HATU ((a) *J. Chem. Soc. Chem Comm.* 1994, 201; (b) *J. Am. Chem. Soc.* 1994, 116, 11580). Additionally, DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4 (3H)-one) and N,N-diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond and provide compounds of Formula I. DEPBT is either purchased from Aldrich or prepared according to the procedure described in *Organic Lett.*, 1999, 1, 91. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used.

EXAMPLES

The following examples illustrate typical syntheses of the compounds of Formula I as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Chemistry Experimental

Typical Procedures and Characterization of Selected Examples:

Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were reported in ppm on the δ scale relative to δTMS=0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), and DMSO-d6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (J) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LCMS Condition:	
Solvent A	5% ACN: 95% Water: 10 mM Ammonium Actetate
Solvent B	95% ACN: 5% Water: 10 mM Ammonium Actetate
Start % B	0
Final % B	100
Gradient Time	2 min
Flow Rate	1 mL/min
Wavelength	220
Solvent Pair	ACN: Water: Ammonium Actetate
Column	Phenomenex LUNA C18, 30 × 2, 3 u

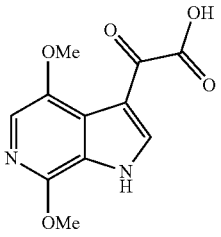
Compounds purified by preparative HPLC were diluted in methanol (1.2 mL) and purified using a Shimadzu LC-8A or LC-10A automated preparative HPLC system.

Typical Procedures and Characterization of Selected Examples:

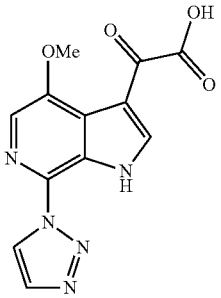
Intermediate ACOCOOH:

Preparation of intermediate ACOCOOH was described in the previous published applications (T. Wang, et al. WO-2001062255 and T. Wang, et al. WO-2002062423). Some examples of ACOCOOH are listed in below.

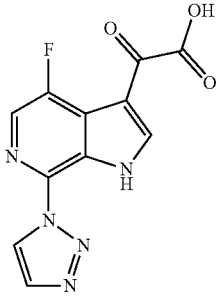
ACOCOOH-01



ACOCOOH-02



ACOCCOH-03



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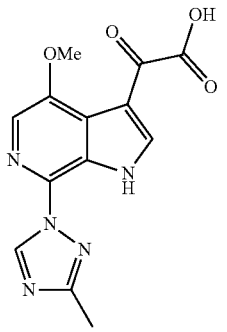
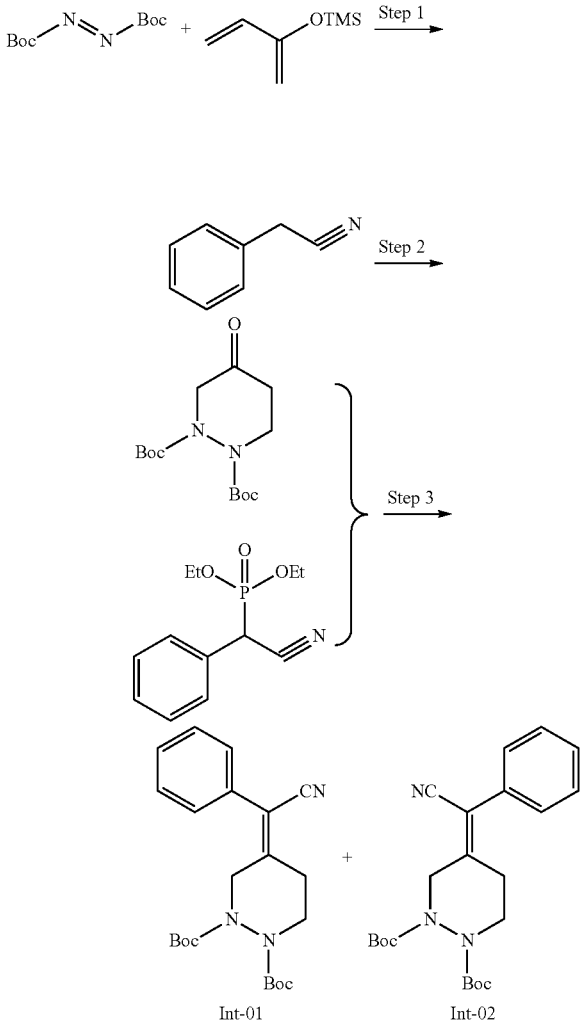
ACOCOOH-04



Preparation of Intermediates Int-01 and Int-02:



Step 1:

To a stirred solution of 2-trimethylsiloxy-1,4-butadiene (10 g) in dry chloroform (100 mL), (E)-di-tert-butyl diazene-1,2-dicarboxylate (12.2 g) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 hours and reaction mass was concentrated. The resulting crude was purified by column chromatography using ethyl acetate\hexane (2.0:8.0) as eluent to afford di-tert-butyl 4-oxopiperazine-1,2-dicarboxylate (6 g) as yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.43-1.55 (s, 18H), 2.94-3.10 (m, 2H), 3.47-3.54 (m, 1H), 3.60-3.75 (m, 1H), 4.32-4.45 (m, 1H), 4.52-4.60 (m, 1H).

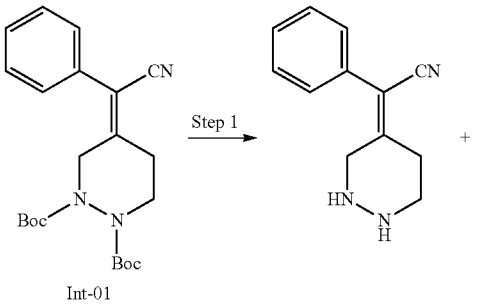
Step 2:

To a stirred solution of benzyl cyanide (2.5 g) in dry tetrahydrofuran (25 mL), slowly added lithium hexamethyl disilazane (26 mL, 1.0M in THF) under nitrogen atmosphere at −78° C. The reaction mixture was stirred at −78° C. for 1 hour and chloro diethyl phosphite (5 g) was added slowly under nitrogen atmosphere at −78° C. The reaction mixture was stirred at −78° C. for about 2 hours and quenched with saturated ammonium chloride solution (25 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure gave crude diethyl cyano(phenyl)methylphosphonate (3 g) as yellow liquid, which was used without any purification. ^{1}H NMR ($CDCl_3$): δ 1.24-1.28 (t, 3H), 1.30-1.33 (t, 3H), 4.14-3.90 (m, 4H), 4.20 (d, 1H), δ 7.45-7.20 (m, 5H).

Step 3:

To a solution of diethyl cyano(phenyl)methylphosphonate (10.0 g) in dry THF (100 mL) under nitrogen, sodium bistrimethylsilyl amide (40 mL, 1M in THF) was added dropwise at 0° C. and the resulting mixture was stirred for 30 minutes, before di-tert-butyl 4-oxopiperazine-1,2-dicarboxylate (10 g) in 25 mL of dry THF was added in dropwise at 0° c. Reaction mixture was stirred at room temperature for 24 hours and the reaction was quenched with saturated ammonium chloride (50 mL), followed by extraction with ethyl acetate (2×50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to get crude product compounds Int-01 & Int-02, which were isolated by preparative HPLC. NMR of Int-01: ^{1}H NMR ($CDCl_3$): δ 1.50-1.53 (bs, 18H), 2.45-2.7 (m, 2H), 3.05-3.15 (m, 1H), 3.85-3.94 (m, 1H), 4.05-4.21 (m, 1H), 5.65-5.82 (m, 1H), 7.28-7.31 (m, 2H), 7.40-7.45 (m, 3H).

Synthesis of Compound 1001, (E)-2-(1-(2-(4-fluoro-7-(1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)piperazin-4-ylidene)-2-phenylacetonitrile



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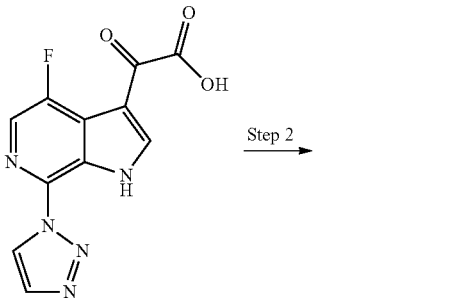
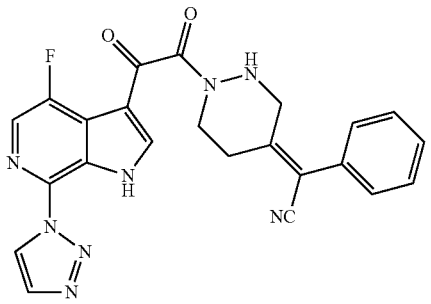




1001

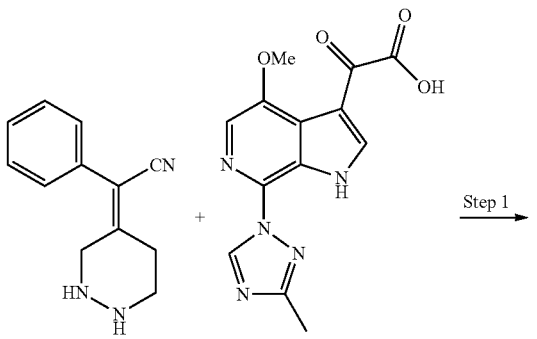
Step 1:

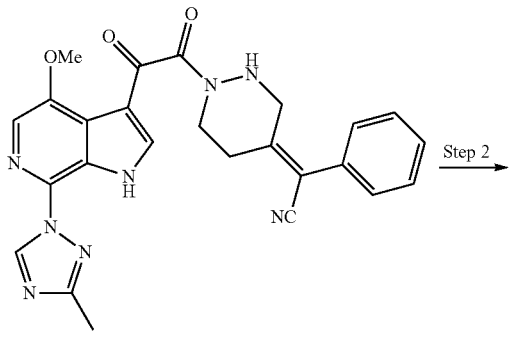
Int-01 (0.3 g) was dissolved in dry DCM (10 mL) and TFA (1 mL) was added in at 0° C. The reaction mixture was stirred at room temperature for 24 hours. The volatiles were completely removed under reduced pressure and the resulting crude was diluted with dichloromethane (10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2×10 mL), brine (20 mL) and dried over Na_2SO_4. Evaporation of solvent gave (E)-2-phenyl-2-(piperazin-4-ylidene)acetonitrile (0.2 g), which was used further without any purification. ^1H NMR ($CDCl_3$): δ 2.65-2.85 (m, 1H), 2.95-3.15 (m, 1H), 3.2-3.4 (m, 1H), 3.60-3.75 (m, 1H), 4.25-4.4 (m, 1H), 4.80-5.1 (m, 1H), 7.23-7.44 (m, 5H).

Step 2:

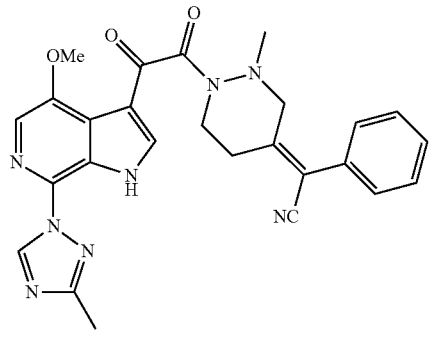
To a stirred solution of 2-(4-fluoro-7-(1H-1,2,3-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (100 mg) in dry DMF (5 mL), (E)-2-phenyl-2-(piperazin-4-ylidene)acetonitrile (80 mg), BOP reagent (240 mg) and DIPEA (0.5 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents was removed under reduced pressure. The resulting oil was diluted with ethyl acetate (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting crude was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1001 (50 mg) as off white solid. ^1H NMR (DMSO-d_6): δ 3.02 (m, 2H), 3.42 (m, 2H), 3.90 (m, 2H), 7.30-7.50 (m, 5H), 8.13 (m, 1H), 8.30 (m, 2H), 9.02 (m, 1H), 12.96 (s, 1H). LCMS: Retention time: 1.51 min/MS $(M+H)^+$ Calcd. 457.1, MS $(M+H)^+$ Observ. 457.3.

Synthesis of Compound 1002, (E)-2-(1-(2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)piperazin-4-ylidene)-2-phenylacetonitrile and Compound 1003, (E)-2-(1-(2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)-2-methylpiperazin-4-ylidene)-2-phenylacetonitrile





1002



1003

Step 1:

To a stirred solution of 2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (100 mg) in dry DMF (5 mL), (E)-2-phenyl-2-(piperazin-4-ylidene)acetonitrile (80 mg), BOP reagent (218 mg) and DIPEA (0.5 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents was removed under reduced pressure. The resulting oil was diluted with ethyl acetate (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was

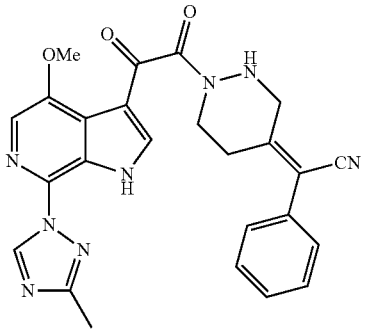
dried over anhydrous Na_2SO_4 and concentrated. The resulting crude was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1002 (50 mg) as off white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.49-2.53 (m, 2H), 2.96 (m, 2H), 3.87-3.91 (m, 2H), 3.93 (s, 3H), 5.54 (s, 1H), 7.32-7.40 (m, 5H), 7.78 (s, 1H), 8.13 (s, 1H), 9.24 (s, 1H). LCMS: Retention time: 1.43 min/MS $(M+H)^+$ Calcd. 483.2, MS $(M+H)^+$ Observ. 483.4.

Step 2:

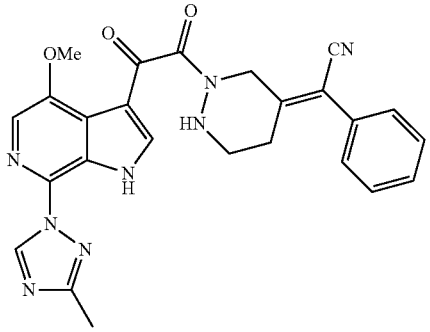
To a stirred solution of 1002 (30 mg) in dry acetonitrile (5 mL), added potassium carbonate (18 mg) under nitrogen atmosphere at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes before methyl iodide (0.05 mL) was added slowly under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 4 hours before being quenched by water (5.0 mL). Aqueous solution was extracted with ethyl acetate (3×5.0 mL). The combined organic layer was washed with brine (5.0 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure gave crude product, which was purified by flash column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1003 (20 mg) as off white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.04-3.11 (t, 2H), 3.50 (s, 3H), 3.54-3.59 (m, 2H), 3.87-3.96 (m, 2H), 4.19 (s, 3H), 7.21-7.23 (m, 2H), 7.34-7.46 (m, 3H), 7.85 (s, 1H), 7.97 (s, 1H), 8.50 (s, 1H). LCMS: Retention time: 1.35 min/MS $(M+H)^+$ Calcd. 497.2, MS $(M+H)^+$ Observ. 497.4.

Synthesis of Compound 1004, (Z)-2-(1-(2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)piperazin-4-ylidene)-2-phenylacetonitrile and Compound 1005, (Z)-2-(2-(2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)piperazin-4-ylidene)-2-phenylacetonitrile

1004



1005



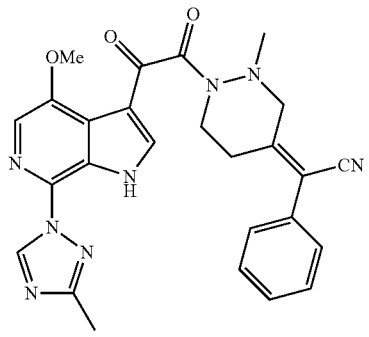
Compounds 1004 and 1005 were prepared via the same process of making compound 1002, by using Int-02 instead of Int-01 as the starting material.

NMR of 1004: ^1H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H), 2.67-2.70 (t, 1H), 3.59-3.61 (d, 2H), 3.70-3.90 (m, 2H), 3.98 (s, 3H), 5.63 (m, 1H), 5.80 (t, 1H), 7.37-7.39 (m, 2H), 7.44-7.51 (m, 3H), 7.86 (s, 1H), 8.20 (s, 1H), 9.24 (s, 1H), 12.32 (bs, 1H). LCMS: Retention time: 1.44 min/MS $(M+H)^+$ Calcd. 483.2, MS $(M+H)^+$ Observ. 483.4.

NMR of 1005: ^1H NMR (400 MHz, DMSO-d_6): δ 2.47-2.48 (s, 3H), 2.66 (m, 2H), 3.3 (m, 2H), 3.98 (s, 3H), 4.65 (m, 2H), 5.46-5.50 (t, 1H), 7.39-7.52 (m, 5H), 7.86 (s, 1H), 8.19 (s, 1H), 9.22 (s, 1H), 12.32 (bs, 1H). LCMS: Retention time: 1.46 min/MS $(M+H)^+$ Calcd. 483.2, MS $(M+H)^+$ Observ. 483.4.

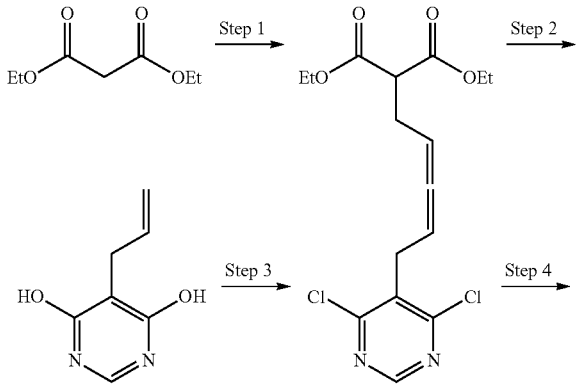
Synthesis of Compound 1006, (Z)-2-(1-(2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetyl)-2-methylpiperazin-4-ylidene)-2-phenylacetonitrile

1006



Compound 1006 was prepared via the same process of making compound 1003, by using 1004 instead of 1002 as the starting material. LCMS: Retention time: 1.37 min/MS $(M+H)^+$ Calcd. 497.2, MS $(M+H)^+$ Observ. 497.4.

Synthesis of Compound 2001, 1-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-(1-methyl-5-phenyl-3,4-dihydropyrimido[4,5-c]pyridazin-2(1H)-yl)ethane-1,2-dione



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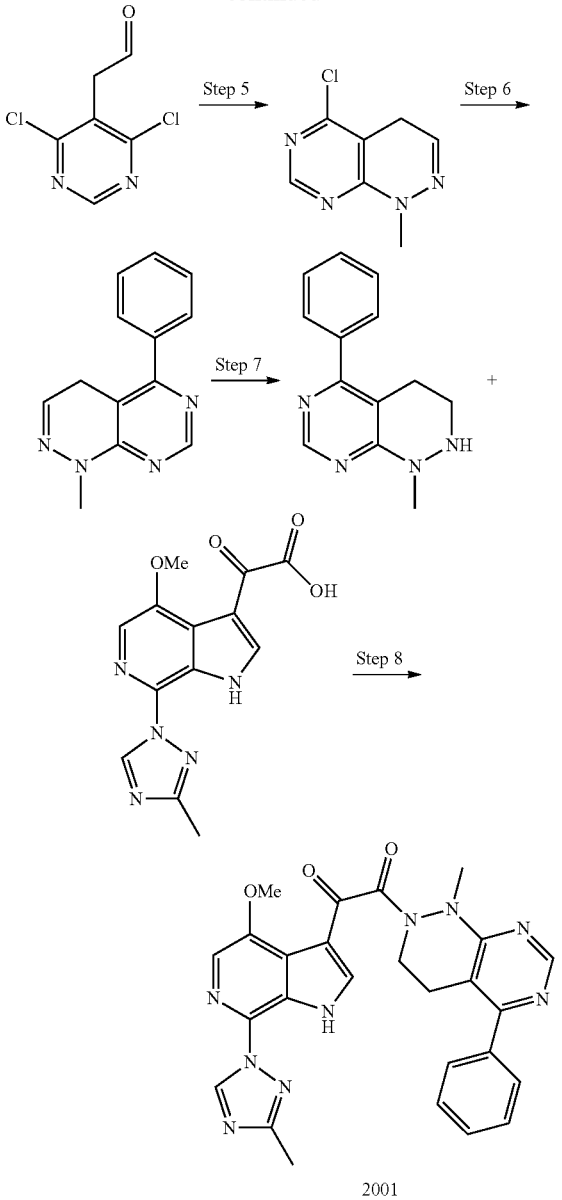


2001

Step 1:

A 500 mL three necked round bottom flask was charged with diethyl malonate (20 g), dry potassium carbonate (43 g) and dry CH_3CN (200 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 10 minutes and allylbromide (23 g) was slowly added to the reaction mixture at room temperature. The reaction mixture was heated to 80° C. for 24 hours. The reaction mixture was cooled to room temperature and filtered through celite bed. The celite bed was washed with acetonitrile (100 mL) and the combined filtrate was concentrated to give diethyl 2-allylmalonate (24 g) as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 6H), 2.61-2.67 (m, 2H), 3.42 (t, 1H), 4.20 (q, 4H), 5.03-5.16 (m, 2H), 5.70-5.85 (m, 1H).

Step 2:

Sodium metal (4.5 g) was added slowly into ethanol (100 mL) in a 500 mL round bottom flask under nitrogen atmosphere. The reaction mixture was stirred at room temperature until all the sodium metal dissolved, before being cooled to 0° C. Diethyl 2-allylmalonate (12 g) was added into the reaction mixture, followed by formamidine acetate (6.24 g) under nitrogen atmosphere at 0° C. The reaction was stirred at room temperature for 24 hours under nitrogen atmosphere, before being quenched by acetic acid (20 mL), followed by water (100 mL). The white precipitate was filtered, washed with water (4×50 mL), methanol (2×50 mL) and dried under vacuum to afford 5-allylpyrimidine-4,6-diol (4 g) as white solid. ^{1}H NMR (DMSO-d_6): δ 2.96 (d, 2H), 4.85 (dd, 1H), 4.91 (dd, 1H), 5.76 (dd, 1H), 7.89 (s, 1H), 11.64 (bs, 2H).

Step 3:

A 100 ml three necked round bottom flask was charged with 5-allylpyrimidine-4,6-diol (4 g) and phosphorusoxychloride (25 mL) under nitrogen atmosphere. The reaction mixture was heated to 80° C. for 3 hours. The reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. The resulting oil was neutralized with saturated $NaHCO_3$ solution and pH was adjusted to 8-9. The aqueous layer was diluted with dichloromethane (100 mL) and was extracted with dichloromethane (2×50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure gave crude compound, which was purified by column chromatography using MeOH/$CHCl_3$ (0.4:9.6) as eluent to afford 5-allyl-4,6-dichloropyrimidine (2.7 g). ^{1}H NMR (DMSO-d_6): δ 3.59-3.61 (d, 2H), 5.00-5.05 (dd, 1H), 5.13-5.16 (dd, 1H), 5.85-5.94 (m, 1H), 8.8 (s, 1H).

Step 4:

To a stirred solution of 5-allyl-4,6-dichloropyrimidine (2.5 g) in dry dioxane (25 mL), N-methyl morpholine N-oxide (2.3 g) and osmium tetroxide (0.85 mL, 25% solution in water) were added. The reaction mixture was stirred at room temperature for 2 hours before being quenched by solid sodium bisulphate. The reaction mixture was filtered through celite bed. The celite bed was washed with dioxane (10 mL). The combined filtrate was taken into a 100 mL three necked round bottom flask and sodium metaperiodate (6 g, in 5 mL water) was added. The reaction mixture was stirred at room temperature for about 3 hours, then diluted with water (30 mL). Aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure gave crude product, which was treated with hexane to offer a solid. The solid obtained was filtered, washed with cold hexane (50 mL) and dried under vacuum to get 2-(4,6-dichloropyrimidin-5-yl) acetaldehyde (1.7 g) as white solid. ^{1}H NMR (DMSO-d_6): δ 4.21 (s, 2H), 8.86 (s, 1H), 9.7 (s, 1H).

Step 5:

To a stirred solution of 2-(4,6-dichloropyrimidin-5-yl)acetaldehyde (600 mg) in dry MeCN (10 mL), methyl hydrazine (154 mg) and sodium acetate (514 mg) were added. The reaction mixture was stirred at room temperature for 3 hours and solvents were removed under reduced pressure. The resulting oil was diluted with ethyl acetate (50 mL), washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting crude product was purified by column chromatography using EtOAc/$CHCl_3$ (0.4:9.6) as eluent to afford 5-chloro-1-methyl-1,4-dihydropyridazino[3,4-d]pyrimidine (310 mg) as white solid. ^{1}H NMR (DMSO-d_6): δ 3.34 (s, 3H), 3.53-3.54 (d, 2H), 6.91-6.93 (t, 1H), 8.38 (s, 1H).

Step 6:

The 5-chloro-1-methyl-1,4-dihydropyridazino[3,4-d]pyrimidine (310 mg), phenyl boronic acid (208 mg) and potassium carbonate (235 mg) were dissolved in toluene (10 mL)

and water (1.0 mL). The reaction mixture was degassed with nitrogen for 30 minutes and $Pd(PPh_3)_4$ (98 mg) was added. The reaction mixture was again degassed with nitrogen for 20 minutes and then heated to 100° C. for 1 hour in a sealed tube. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (2×20 mL). The combined filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting crude product was purified by column chromatography using MeOH/$CHCl_3$ (1.0:9.0) as eluent to afford 1-methyl-5-phenyl-1,4-dihydropyrimido[4,5-c]pyridazine (350 mg) as off white solid. ^1H NMR (DMSO-d_6): δ 3.41 (s, 3H), 3.52-3.53 (d, 2H), 6.86 (t, 1H), 7.47-7.49 (m, 3H), 7.56-7.60 (m, 2H), 8.66 (s, 1H).

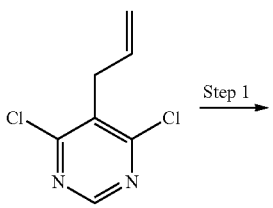
Step 7:

To a stirred solution of 1-methyl-5-phenyl-1,4-dihydropyrimido[4,5-c]pyridazine (350 mg) in dry methanol (15.0 mL), sodium borohydride (296 mg, 7.81 mmol) was added slowly, followed by boric acid (480 mg) under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by column chromatography using EtOAc/hexane (1.4:8.6) as eluent to afford 1-methyl-5-phenyl-1,2,3,4-tetrahydropyrimido[4,5-c] pyridazine (130 mg) as gummy liquid. ^1H NMR (DMSO-d_6): δ 2.66-2.69 (t, 2H), 2.88-2.91 (t, 2H), 3.22 (s, 3H), 5.46-5.50 (t, 1H), 7.41-7.47 (m, 3H), 7.53-7.55 (m, 2H), 8.36 (s, 1H).

Step 8:

To a stirred solution of 2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (123 mg) in dry DMF (5 mL), 1-methyl-5-phenyl-1,2,3,4-tetrahydropyrimido[4,5-c]pyridazine (130 mg), BoP reagent (254 mg) and DIPEA (0.3 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography using MeOH\$CHCl_3$ (0.2:9.8) as eluent to afford 2001 (20 mg) as off white solid. ^1H NMR (400 MHz, DMSO-d6): δ 2.45 (s, 3H), 2.86-2.94 (m, 2H), 3.25 (s, 3H), 3.57-3.75 (m, 1H), 3.87-3.99 (m, 1H), 4.00 (s, 3H), 7.51-7.65 (m, 5H), 7.87 (s, 1H), 8.07-8.18 (m, 1H), 8.58-8.66 (m, 1H), 9.12 (s, 1H), 12.10 (bs, 1H). LCMS: Retention time: 1.42 min/MS $(M+H)^+$ Calcd. 510.2, MS $(M+H)^+$ Observ. 510.4.

Synthesis of Compound 2002, 1-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c] pyridin-3-yl)-2-(1-methyl-5-(pyridin-2-yl)-3,4-dihydropyrimido[4,5-c]pyridazin-2(1H)-yl)ethane-1,2-dione



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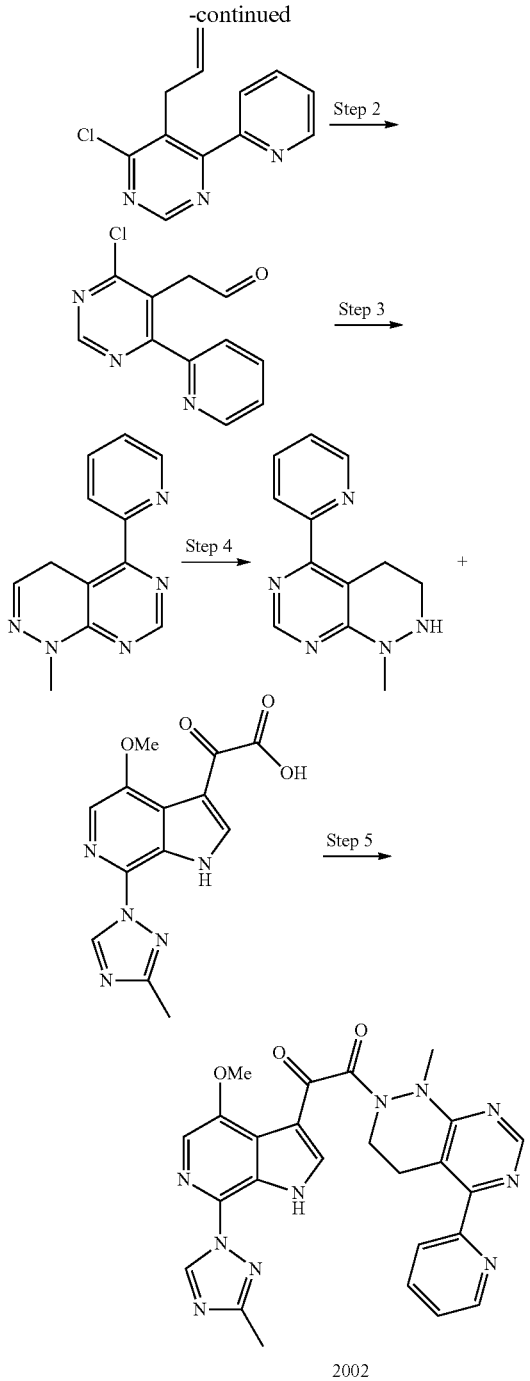


2002

Step 1:

The 5-allyl-4,6-dichloropyrimidine (2 g) and 2-(tributylstannyl) pyridine (6.1 g) were dissolved in dry DMF (1.0 mL). The reaction mixture was degassed with nitrogen for 30 minute and $Pd(PPh_3)_4$ (615 mg) was added. The reaction mixture was again degassed with nitrogen for 20 minutes before being irradiated under microwave at 160° C. for 30 minutes. The reaction mixture was cooled to room temperature, filtered through a celite pad and washed with ethyl acetate (2×50 mL). The combined filtrate was washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography using EtOAc/

hexane (0.4:9.6) as eluent to afford 5-allyl-4-chloro-6-(pyridin-2-yl)pyrimidine (1 g) as off white solid. ^{1}H NMR (DMSO-d_6): δ 3.80-3.82 (d, 2H), 4.83-4.89 (dd, 1H), 4.90-5.00 (dd, 1H), 5.82-5.88 (m, 1H), 7.53-7.57 (m, 1H), 7.90-8.04 (m, 2H), 8.69-8.71 (d, 1H), 9.0 (s, 1H).

Step 2:

To a stirred solution of 5-allyl-4-chloro-6-(pyridin-2-yl) pyrimidine (1 g) in dry dioxane (10 mL), N-methyl morpholine N-oxide (0.75 g) and osmium tetroxide (0.35 mL, 25% solution in water) were added. The reaction mixture was stirred at room temperature for 2 hours before being quenched by solid sodium bisulphate. The reaction mixture was filtered through celite bed and the celite bed was washed with dioxane (5 mL). The combined filtrate was taken into a 100 mL three necked round bottom flask and sodium metaperiodate (2.3 g, in 5 mL water) was added. The reaction mixture was stirred at room temperature for 3 hours and then diluted with water (30 mL). Aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure gave crude 2-(4-chloro-6-(pyridin-2-yl)pyrimidin-5-yl)acetaldehyde (0.7 g) which was used as was. ^{1}H NMR (DMSO-d_6): δ 4.12 (s, 2H), 7.53-7.55 (m, 1H), 7.88-8.01 (m, 2H), 8.66-8.69 (d, 1H), 8.97 (s, 1H), 9.79 (s, 1H).

Step 3:

To a stirred solution of 2-(4-chloro-6-(pyridin-2-yl)pyrimidin-5-yl)acetaldehyde (600 mg) in dry MeCN (10 mL), methyl hydrazine (181 mg) and sodium acetate (422 mg) were added. The reaction mixture was stirred at room temperature for 3 hours and solvents were removed under reduced pressure. The resulting crude was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1-methyl-5-(pyridin-2-yl)-1,4-dihydropyrimido[4,5-c]pyridazine (350 mg) as white solid. ^{1}H NMR (DMSO-d_6): δ 3.41 (s, 3H), 3.93-3.94 (d, 2H), 6.92-6.94 (t, 1H), 7.47-7.51 (m, 1H), 7.94-7.99 (m, 1H), 8.00-8.10 (m, 1H), 8.67-8.69 (d, 2H).

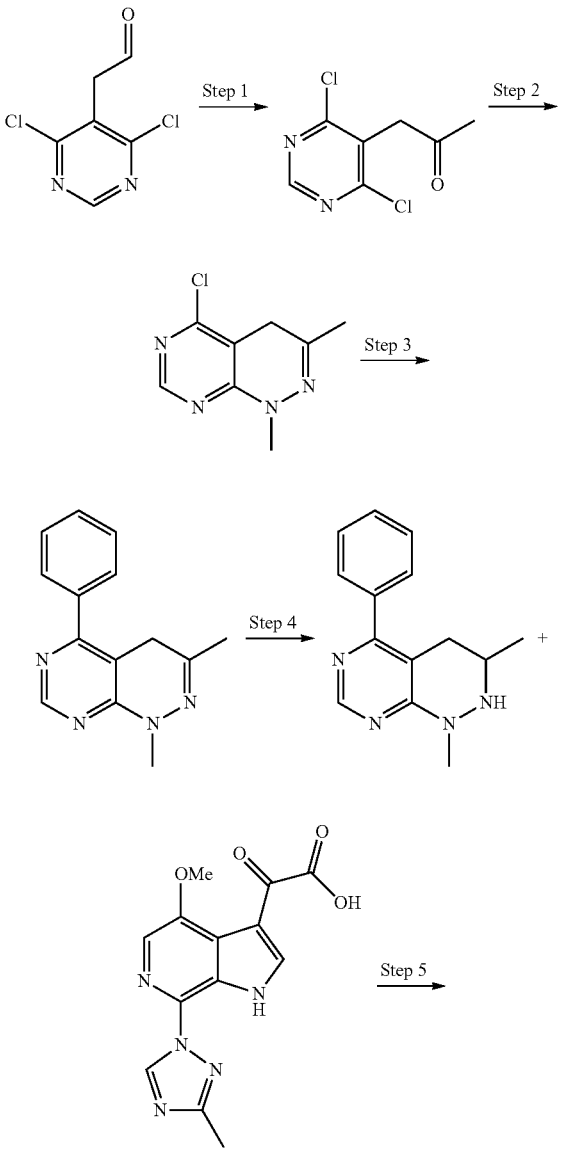
Step 4:

To a stirred solution of 1-methyl-5-(pyridin-2-yl)-1,4-dihydropyrimido[4,5-c]pyridazine (100 mg) in dry THF (5.0 mL), sodium borohydride (84 mg) was slowly added, followed by boric acid (137 mg) under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 2 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1-methyl-5-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimido[4,5-c]pyridazine (35 mg) as white solid. ^{1}H NMR (DMSO-d_6): δ 2.92-2.93 (m, 4H), 3.22 (s, 3H), 5.49 (t, 1H), 7.41-7.44 (t, 1H), 7.90-7.92 (m, 2H), 8.38 (s, 1H), 8.62-8.64 (d, 1H).

Step 5:

To a stirred solution of 2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (46 mg) in dry DMF (5 mL), 1-methyl-5-(pyridin-2-yl)-1,2,3,4-tetrahydropyrimido[4,5-c]pyridazine (35 mg), 2-chloro-1,3-dimethyl imidazolium chloride (54 mg) and DIPEA (0.16 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using MeOH\$CHCl_3$ (1.3:8.7) as eluent to afford 2002 (20 mg) as white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 2.45 (s, 3H), 3.21-3.29 (m, 2H), 3.32 (s, 3H), 3.54-3.77 (m, 2H), 3.97 (s, 3H), 7.44-7.52 (m, 1H), 7.82-7.86 (d, 1H), 7.93-8.03 (m, 3H), 8.58-8.66 (m, 2H), 9.20 (s, 1H), 12.37 (bs, 1H). LCMS: Retention time: 1.32 min/MS $(M+H)^+$ Calcd. 511.2, MS $(M+H)^+$ Observ. 511.4.

Synthesis of Compound 2003, 1-(1,3-dimethyl-5-phenyl-3,4-dihydropyrimido[4,5-c]pyridazin-2(1H)-yl)-2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)ethane-1,2-dione



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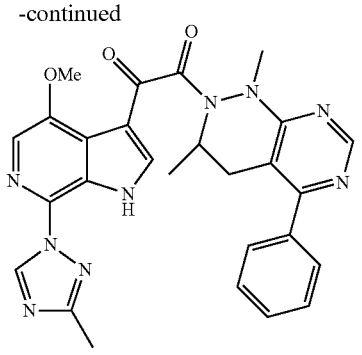


2003

Step 1:

A 500 mL two necked round bottom flask was charged with 2-(4,6-dichloropyrimidin-5-yl)acetaldehyde (1.2 g), dry diethyl ether (80 mL) and dry THF (80 mL). The reaction mixture was cooled to 0° C. and diazomethane solution in diethyl ether (30 mL) was slowly added under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 24 hours under nitrogen atmosphere before being quenched by acetic acid (20 mL), followed by water (100 mL). Aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure gave crude 1-(4,6-dichloropyrimidin-5-yl)propan-2-one (0.94 g) which was used as was. ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H), 4.19 (s, 2H), 8.85 (s, 1H).

Step 2:

To a stirred solution of 1-(4,6-dichloropyrimidin-5-yl)propan-2-one (940 mg) in dry MeCN (10 mL), methyl hydrazine (232 mg) and sodium acetate (715 mg) were added. The reaction mixture was stirred at room temperature for 24 hours before being quenched with water (100 mL). Aqueous layer was extracted with dichloromethane (2×25 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure gave crude 5-chloro-1,3-dimethyl-1,4-dihydropyridazino[3,4-d]pyrimidine (1.1 g) as white solid which was used as was. ^{1}H NMR (DMSO-d_6): δ 2.06 (s, 3H), 3.2 (s, 3H), 3.55 (s, 2H), 8.33 (s, 1H).

Step 3:

The 5-chloro-1,3-dimethyl-1,4-dihydropyridazino[3,4-d]pyrimidine (1.1 g), phenyl boronic acid (682 mg) and potassium carbonate (771 mg) were dissolved in toluene (15 mL) and water (1.5 mL). After the reaction mixture was degassed with nitrogen for 30 minute, $Pd(PPh_3)_4$ (323 mg) was added. The reaction mixture was again degassed with nitrogen for 20 minutes and then heated to 100° C. for 3 hours in a sealed tube. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (2×20 mL). The combined filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using MeOH/$CHCl_3$ (0.8:9.2) as eluent to afford 1,3-dimethyl-5-phenyl-1,4-dihydropyridazino[3,4-d]pyrimidine (500 mg) as colorless viscous liquid. ^{1}H NMR (DMSO-d_6): δ 1.89 (s, 3H), 3.37 (s, 3H), 3.52 (s, 2H), 7.47-7.57 (m, 5H), 8.60 (s, 1H).

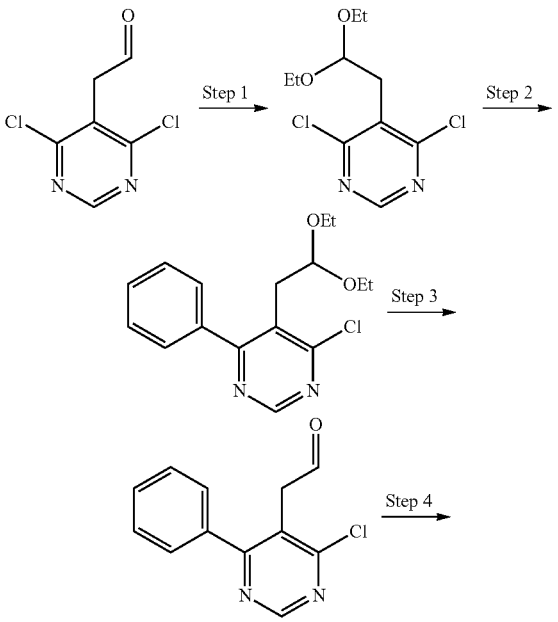
Step 4:

To a stirred solution of 1,3-dimethyl-5-phenyl-1,4-dihydropyridazino[3,4-d]pyrimidine (260 mg) in dry THF (15 mL), sodium borohydride (414 mg) was slowly added, followed by boric acid (670 mg) under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 2 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 1,3-dimethyl-5-phenyl-1,2,3,4-tetrahydropyridazino[3,4-d]pyrimidine (95 mg) as colorless oily liquid. ^{1}H NMR (DMSO-d_6): δ 1.00-1.02 (d, 3H), 2.62-2.71 (t, 2H), 3.22 (s, 3H), 3.31-3.34 (m, 1H), 5.28-5.31 (d, 1H), 7.43-7.51 (m, 5H), 8.36 (s, 1H).

Step 5:

To a stirred solution of 2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (100 mg) in dry DMF (5 mL), 1,3-dimethyl-5-phenyl-1,2,3,4-tetrahydropyridazino[3,4-d]pyrimidine (80 mg), 2-chloro-1,3-dimethyl imidazolium chloride (56 mg) and DIPEA (0.2 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using MeOH\$CHCl_3$ (0.3:9.7) as eluent to afford 2003 (15 mg) as off white solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.02-1.09 (m, 3H), 2.49 (s, 3H), 3.36-3.37 (m, 2H), 3.56 (s, 3H), 4.00 (s, 3H), 4.35-4.41 (m, 1H), 7.47-7.67 (m, 5H), 7.90 (s, 1H), 8.12 (m, 1H), 8.55 (m, 1H), 9.12 (s, 1H), 12.05-12.15 (bs, 1H). LCMS: Retention time: 1.46 min/MS $(M+H)^+$ Calcd. 524.2, MS $(M+H)^+$ Observ. 524.4.

Synthesis of Compound 2004, 1-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-(5-phenyl-3,4-dihydropyrimido[4,5-c]pyridazin-2(1H)-yl)ethane-1,2-dione



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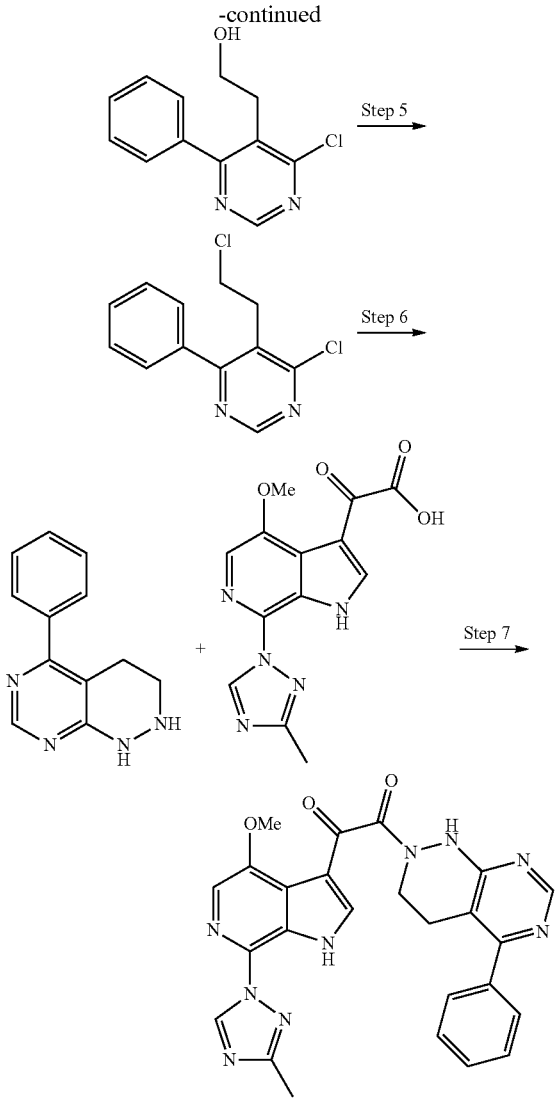


2004

Step 1:

To a stirred solution of 2-(4,6-dichloropyrimidin-5-yl)acetaldehyde (1 g) in dry ethanol (10 mL), ammonium chloride (140 mg) was added. The reaction mixture was stirred at 80° C. for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to gave crude 4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine (1.1 g) as viscous liquid, which was used as was. ^1H NMR (DMSO-d_6): δ 1.11-1.13 (t, 6H), 2.85-2.87 (d, 2H), 3.41-3.45 (q, 4H), 4.58-4.61 (t, 1H), 9.44 (s, 1H).

Step 2:

The 4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine (1.1 g), phenyl boronic acid (500 mg) and potassium carbonate (556 mg) were dissolved in toluene (15 mL) and water (1.5 mL). The reaction mixture was degassed with nitrogen for 30 minute and then $Pd(PPh_3)_4$ (230 mg) was added. The reaction mixture was again degassed with nitrogen for 20 minutes before heated to 100° C. for 3 hours in a sealed tube. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (2×20 mL). The combined filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using EtOAc/hexane (0.5:9.5) as eluent to afford 4-chloro-5-(2,2-diethoxyethyl)-6-phenylpyrimidine (800 mg) as colorless viscous liquid. ^1H NMR (DMSO-d_6): δ 1.07-1.10 (t, 6H), 3.21-3.23 (d, 2H), 3.32-3.36 (q, 2H), 3.37-4.00 (q, 2H), 4.79-4.81 (t, 1H), 7.47-7.49 (m, 3H), 7.63-7.66 (m, 2H), 8.91 (s, 1H).

Step 3:

To a stirred solution of 4-chloro-5-(2,2-diethoxyethyl)-6-phenylpyrimidine (800 mg) in dry THF (10 mL), concentrated HCl (2.0 mL) was added. The reaction mixture was stirred at 45° C. for 1 hour and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using MeOH\$CHCl_3$ (0.1:9.9) as eluent to afford 2-(4-chloro-6-phenylpyrimidin-5-yl)acetaldehyde (450 mg) as white solid. ^1H NMR (DMSO-d_6): δ 4.04 (s, 2H), 7.42-7.53 (m, 5H), 9.02 (s, 1H), 9.72 (s, 1H).

Step 4:

To a stirred solution of 2-(4-chloro-6-phenylpyrimidin-5-yl)acetaldehyde (450 mg) in dry methanol (10 mL), sodium borohydride (110 mg) was slowly added under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 2 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue which was purified by column chromatography using MeOH/$CHCl_3$ (0.2:9.8) as eluent to afford 2-(4-chloro-6-phenylpyrimidin-5-yl)ethanol (340 mg) as colorless oily liquid. ^1H NMR (DMSO-d_6): δ 2.89-2.94 (t, 2H), 3.53-3.58 (t, 2H), 4.81-4.85 (t, 1H), 7.50-7.61 (m, 5H), 8.92 (s, 1H).

Step 5:

To a stirred solution of 2-(4-chloro-6-phenylpyrimidin-5-yl)ethanol (340 mg) in dry chloroform (10 mL), phosphorus oxy chloride (2 mL) was slowly added under nitrogen atmosphere at 0° C. The reaction mixture was stirred at room temperature for 2 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to gave crude 4-chloro-5-(2-chloroethyl)-6-phenylpyrimidine (150 mg) as viscous liquid, which was used as was. ^1H NMR (DMSO-d_6): δ 2.89-2.94 (t, 2H), 3.54-3.55 (t, 2H), 7.48-7.59 (m, 5H), 8.91 (s, 1H).

Step 6:

To a stirred solution of 4-chloro-5-(2-chloroethyl)-6-phenylpyrimidine (150 mg) in dry THF (10 mL), hydrazine (5 mL, 1.0M in THF) was slowly added under nitrogen atmosphere at room temperature. The reaction mixture was stirred at 60° C. for 5 hours and solvents were removed under reduced pressure. The resulting oil was purified by column chromatography using MeOH/$CHCl_3$ (0.5:9.5) as eluent to afford 5-phenyl-1,2,3,4-tetrahydropyridazino[3,4-d]pyrimidine (45 mg) as colorless oily liquid. ^1H NMR (DMSO-d_6): δ 2.63-2.65 (t, 2H), 2.79-2.81 (t, 2H), 4.93-4.97 (t, 1H), 7.43-7.48 (m, 3H), 7.56-7.59 (m, 2H), 8.29 (s, 1H), 8.69 (s, 1H).

Step 7:

To a stirred solution of 2-(4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-2-oxoacetic acid (56 mg) in dry DMF (5 mL), 5-phenyl-1,2,3,4-tetrahydropyridazino[3,4-d]pyrimidine (40 mg), BoP reagent (79

mg) and DIPEA (0.2 mL) were added. The reaction mixture was stirred at room temperature for 24 hours and solvents were removed under reduced pressure. The resulting oil was diluted with dichloromethane (50 mL), washed with 10% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using MeOH\$CHCl_3$ (0.2:9.8) as eluent to afford 2004 (20 mg) as off white solid. ^1H NMR (400 MHz, DMSO-d6): δ 2.45 (s, 3H), 2.88-2.92 (m, 2H), 3.59-3.65 (m, 1H), 3.77-3.89 (m, 1H), 3.97 (s, 3H), 7.52-7.63 (m, 5H), 7.90 (s, 1H), 8.47-8.53 (m, 1H), 8.58 (s, 1H), 9.13 (s, 1H), 12.10 (bs, 1H). LCMS: Retention time: 1.32 min/MS $(M+H)^+$ Calcd. 496.2, MS $(M+H)^+$ Observ. 496.4.

Biology Data for the Examples

"μM" means micromolar;
"mL" means milliliter;
"μl" means microliter;
"mg" means milligram;

The materials and experimental procedures used to obtain the results reported in Table 1 are described below.

Cells:

Virus production—Human embryonic Kidney cell line, 293T (HEK 293T), was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, Calif.) containing 10% fetal bovine serum (FBS, Sigma, St. Louis, Mo.). The human T-cell leukemia cell MT2 (AIDS Research and Reference Reagent Program, Cat. 237) was propagated in RPMI 1640 (Invitrogen, Carlsbad, Calif.) containing 10% fetal bovine serum (FBS, Hyclone, Logan, Utah)

Virus infection—Single-round infectious reporter virus was produced by co-transfecting HEK 293T cells with plasmide expressing the HIV-1 LAI envelope along with a plasmid containing an HIV-1 LAI proviral cDNA with the envelope gene replaced by a firefly luciferase reporter gene (Chen et al., Ref 41). Transfections were performed using lipofectAMINE PLUS reagent as described by the manufacturer (Invitrogen, Carlsbad, Calif.).

Experimental Procedure

1. MT2 cells were plated in black, 384 well plates at a cell density of 5×10^3 cells per well in 25 μl RPMI 1640 containing 10% FBS.
2. Compound (diluted in dimethylsulfoxide and growth medium) was added to cells at 12.5 μl/well, so that the final assay concentration would be ≤50 nM.
3. 12.5 μl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 50 μl per well.
4. Virus-infected cells were incubated at 37 degrees Celsius in a CO_2 incubator and harvested 72 h after infection.
5. Viral infection was monitored by measuring luciferase expression in the infected cells using a luciferase reporter gene assay kit (Steady-Glo, Promega, Madison, Wis.) as described by the manufacturer. Luciferase activity was then quantified by measuring luminescence using an EnVision Multilabel Plate Readers (PerkinElmer, Waltham, Mass.).
6. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.
7. An EC_{50} provides a method for comparing the antiviral potency of the compounds of this disclosure. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four parameter logistic model (model 205). The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

TABLE 1

Biological Data Key for EC_{50}s

Compounds with EC_{50} > 0.5 μM	Compounds with EC_{50} < 0.5 μM
Group B	Group A

TABLE 2

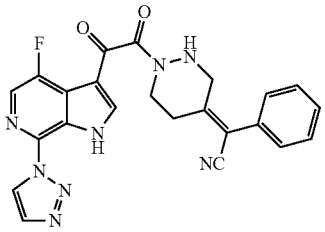
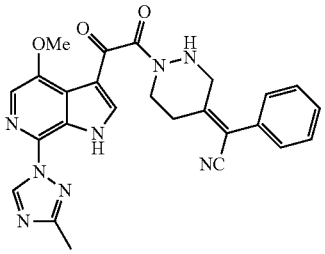
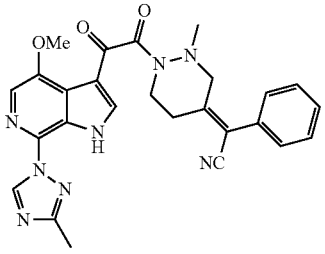
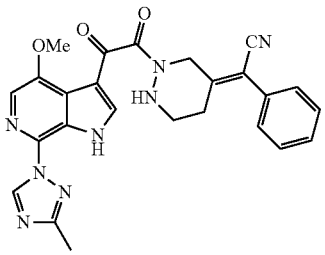
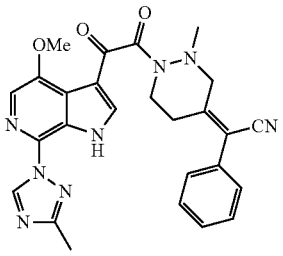
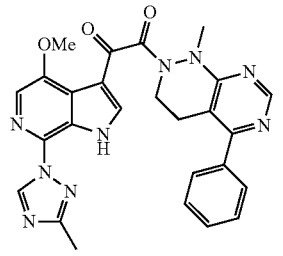
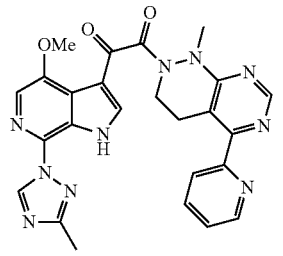
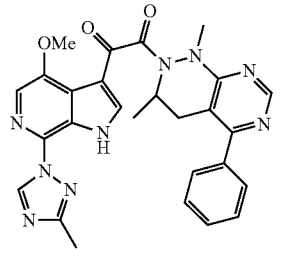
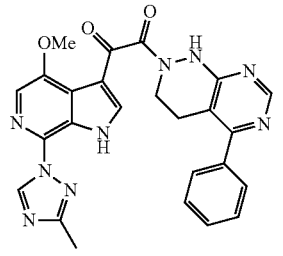
Compd. Number	Structure	EC_{50} Group from Table 1
1001		A
1002		A 0.29 nM
1003		A
1005		A 25.62 nM

TABLE 2-continued

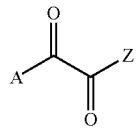
Compd. Number	Structure	EC_{50} Group from Table 1
1006		A 455.60 nM
2001		A
2002		A
2003		A
2004		A

The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims

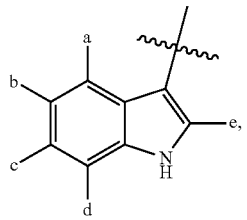
What is claimed is:

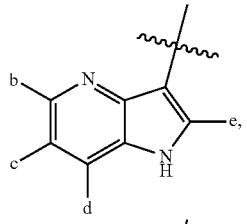
1. A compound of Formula I, including pharmaceutically acceptable salts thereof:

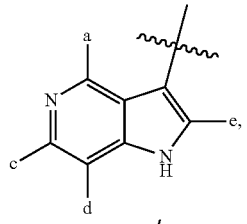
I

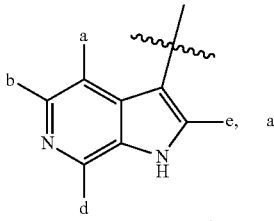


wherein A is selected from the group consisting of:

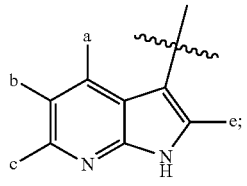








and



wherein

a, b, c, d and e are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^{56}$, XR^{57}, NA^1A^2, $C(O)R^7$, $C(O)NR^{55}R^{56}$, B, Q, and E;

B is selected from the group consisting of —$C(=NR^{46})(R^{47})$, $C(O)NR^{40}R^{41}$, aryl, heteroaryl, heteroalicyclic, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $C(O)R^7$, XR^{8a}, $(C_{1-6})alkylNR^{40}R^{41}$, $(C_{1-6})alkylCOOR^{8b}$;

wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group F; wherein aryl is napthyl or

substituted phenyl; wherein heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for a mono cyclic system and up to 12 atoms in a fused bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is a 3 to 7 membered mono cyclic ring which may contain from 1 to 2 heteroatoms in the ring skeleton and which may be fused to a benzene or pyridine ring;

Q is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6}) alkyl and (C_{2-6})alkenyl are optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from the group consisting of $C(O)NR^{55}R^{56}$, hydroxy, cyano and XR^{57};

E is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl and (C_{2-6})alkenyl; wherein said (C_{1-6}) alkyl and (C_{2-6})alkenyl are independently optionally substituted with a member selected from the group consisting of phenyl, heteroaryl, SMe, SPh, —C(O) $NR^{56}R^{57}$, $C(O)R^{57}$, $SO_2(C_{1-6})$alkyl and SO_2Ph; wherein heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms;

F is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, (C_{1-6})thioalkoxy, cyano, halogen, nitro, —$C(O)R^{57}$, benzyl, —$NR^{42}C(O)$—(C_{1-6})alkyl, —$NR^{42}C(O)$—(C_{3-6})cycloalkyl, —$NR^{42}C(O)$-aryl, —$NR^{42}C(O)$-heteroaryl, —$NR^{42}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{42}S(O)_2$—(C_{1-6})alkyl, —$NR^{42}S(O)_2$—(C_{3-6})cycloalkyl, —$NR^{42}S(O)$2-aryl, —$NR^{42}S(O)_2$-heteroaryl, —$NR^{42}S(O)$2-heteroalicyclic, $S(O)_2(C_{1-6})$ alkyl, $S(O)_2$aryl, —S(O)2 $NR^{42}R^{43}$, $NR^{42}R^{43}$, (C_{1-6}) alkyl$C(O)NR^{42}R^{43}$, $C(O)NR^{42}R^{43}$, $NHC(O)NR^{42}R^{43}$, $OC(O)NR^{42}R^{43}$, $NHC(O)OR^{54}$, (C_{1-6})alkyl$NR^{42}R^{43}$, $COOR^{54}$, and (C_{1-6})alkyl$COOR^{54}$; wherein said (C_{1-6}) alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, (C_{1-6})alkoxy, and aryloxy, are optionally substituted with one to nine same or different halogens or from one to five same or different substituents selected from the group G; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

G is selected from the group consisting of (C_{1-6})alkyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, aryloxy, cyano, halogen, nitro, —$C(O)R^{57}$, benzyl, —$NR^{48}C(O)$—(C_{1-6})alkyl, —$NR^{48}C(O)$—(C_{3-6})cycloalkyl, —$NR^{48}C(O)$-aryl, —$NR^{48}C(O)$-heteroaryl, —$NR^{48}C(O)$-heteroalicyclic, a 4, 5, or 6 membered ring cyclic N-lactam, —$NR^{48}S(O)_2$—(C_{1-6})alkyl, —$NR^{48}S(O)_2$—(C_{3-6})cycloalkyl, —$NR^{48}S(O)$2-aryl, —$NR^{48}S(O)_2$-heteroaryl, —$NR^{48}S(O)$2-heteroalicyclic, sulfinyl, sulfonyl, sulfonamide, $NR^{48}R^{49}$, (C_{1-6})alkyl $C(O)NR^{48}R^{49}$, $C(O)NR^{48}R^{49}$, $NHC(O)NR^{48}R^{49}$, $OC(O)NR^{48}R^{49}$, $NHC(O)OR^{54'}$, (C_{1-6})alkyl$NR^{48}R^{49}$, $COOR^{54}$, and (C_{1-6})alkyl-$COOR^{54}$; wherein aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 7 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^7 is selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic; wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or with from one to three same or different substituents selected from the group F;

wherein for R^7, R^8, R^{8a}, R^{8b} aryl is phenyl; heteroaryl is a mono or bicyclic system which contains from 3 to 7 ring atoms for mono cyclic systems and up to 10 atoms in a bicyclic system, including from 1 to 4 heteroatoms; wherein heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^8 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, (C_{3-7})cycloalkenyl, (C_{2-6})alkynyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F or (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R^{8a} is a member selected from the group consisting of aryl, heteroaryl, and heteroalicyclic;

wherein each member is independently optionally substituted with one to six same or different halogens or from one to five same or different substituents selected from the group F;

R^{8b} is selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl;

X is selected from the group consisting of NH or NCH_3, O, and S;

R^{40} and R^{41} are independently selected from the group consisting of

(a) hydrogen; (b) (C_{1-6})alkyl or (C_{3-7})cycloalkyl substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F or different functional groups: (C_{1-6}) alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group

consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; and (c) (C_{1-6})alkoxy, aryl, heteroaryl or heteroalicyclic;

or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group F; wherein for R^{40} and R^{41} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine; provided when B is C(O)$NR^{40}R^{41}$, at least one of R^{40} and R^{41} is not selected from groups (a) or (b);

R^{42} and R^{43} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, allyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl and heteroalicyclic; or R^{42} and R^{43} taken together with the nitrogen to which they are attached form a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, 4-NMe piperazine, piperidine, azepine, and morpholine; and wherein said (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{3-7})cycloalkyl, aryl, heteroaryl, and heteroalicyclic are optionally substituted with one to three same or different halogens or from one to two same or different substituents selected from the group G or different functional groups: (C_{1-6})alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl; wherein for R^{42} and R^{43} aryl is phenyl; heteroaryl is a monocyclic system which contains from 3 to 6 ring atoms, including from 1 to 4 heteroatoms; heteroalicyclic is a member selected from the group consisting of aziridine, azetidine, pyrrolidine, piperazine, piperidine, tetrahydrofuran, tetrahydropyran, azepine, and morpholine;

R^{46} is selected from the group consisting of H, phenyl, aryl, heteroaryl and (C_{1-6})alkyl, OR^{57}, and $NR^{55}R^{56}$;

R^{47} is selected from the group consisting of H, amino, hydroxyl, phenyl, aryl, heteroaryl and (C_{1-6})alkyl;

R^{48} and R^{49} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, phenyl, aryl and heteroaryl;

R^{50} is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, and benzyl; wherein each of said (C_{1-6})alkyl, (C_{3-7})cycloalkyl and benzyl are optionally substituted with one to three same or different (C_{1-6}) alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl

R^{54} is selected from the group consisting of hydrogen and (C_{1-6})alkyl;

$R^{54'}$ is (C_{1-6})alkyl;

R^{55} and R^{56} are independently selected from the group consisting of hydrogen and (C_{1-6})alkyl; and

R^{57} is selected from the group consisting of hydrogen, (C_{1-6})alkyl, aryl, heteroaryl; and

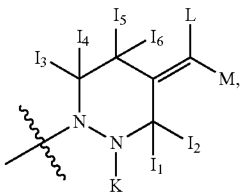
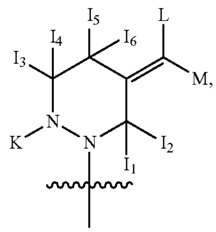
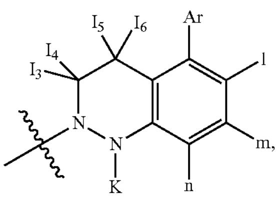
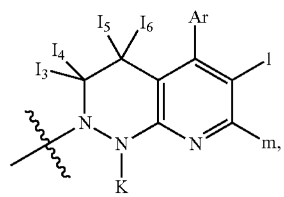
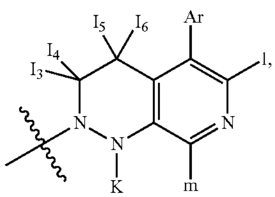
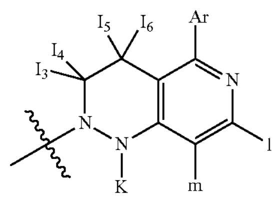
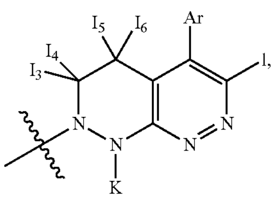
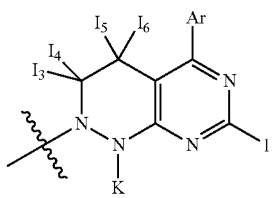
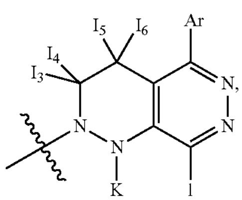
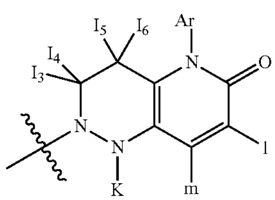
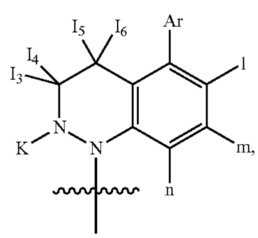
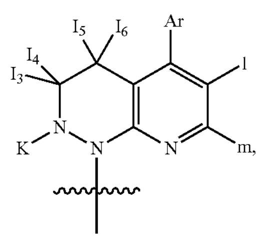
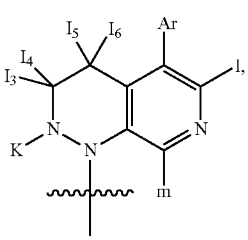
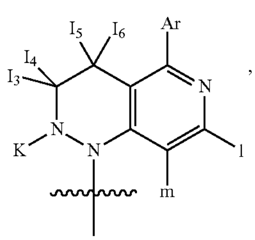
A^1 and A^2 are independently selected from hydrogen, (C_{1-6})alkyl, aryl, heteroaryl, $SO2D^1$, $SO2ND^2D^3$, COD^4, $COCOD^4$, $COOD^4$, $COND^5D^6$, $COCOND^5D^6$, $COCOOD^4$, $C(=ND^7)D^8$, $C(=ND^9)ND^{10}D^{11}$;

A^1 and A^2 can either never connect with each other, or conjoin to form a ring structure;

D^1, D^2, D^3, D^4, D^5, D^6, D^7, D^8, D^9, D^{10}, and D^{11} are each independently selected from the group consisting of H, C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl; provided the carbon atoms which comprise the carbon-carbon double bond of said C_3-C_{20} alkenyl or the carbon-carbon triple bond of said C_3-C_{20} alkynyl are not the point of attachment to the nitrogen to which D^2, D^3, D^5, D^6, D^7, D^9, D^{10}, and D^{11} is attached; wherein said C_1-C_{50} alkyl, C_3-C_{50} cycloalkyl, C_3-C_{50} alkenyl, C_4-C_{50} cycloalkenyl, aryl, phenyl, heteroaryl, C_3-C_{50} amide and C_3-C_{50} ether is optionally substituted with one to three same or different of the following functionalities: (C_{1-6}) alkyl, (C_{3-6})cycloalkyl, cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydra-

zine, peroxide and steroid, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic;

Z is selected from the group consisting of:

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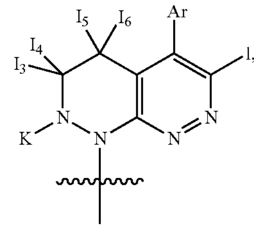
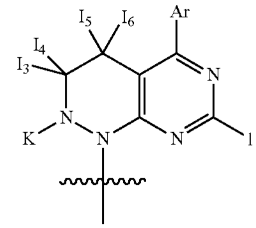
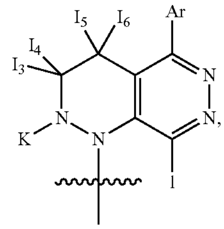
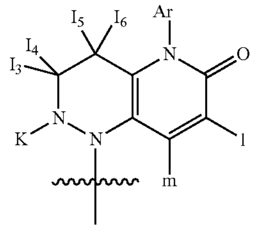
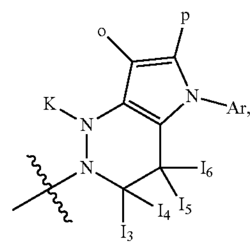
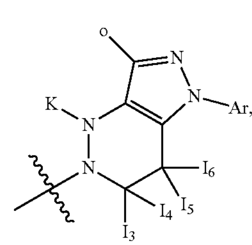
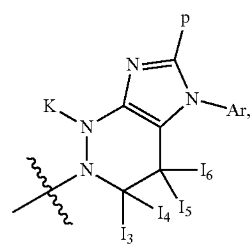
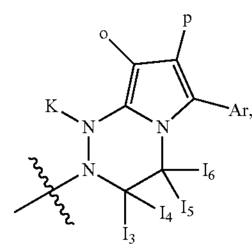
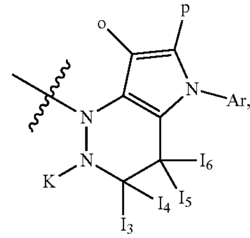
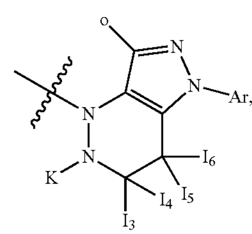
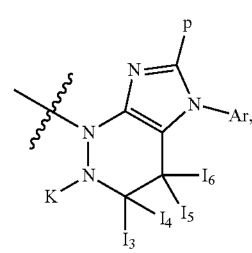
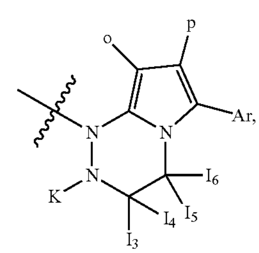
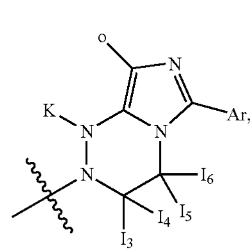
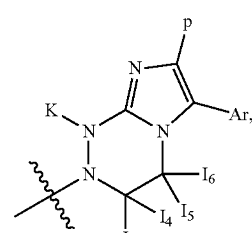

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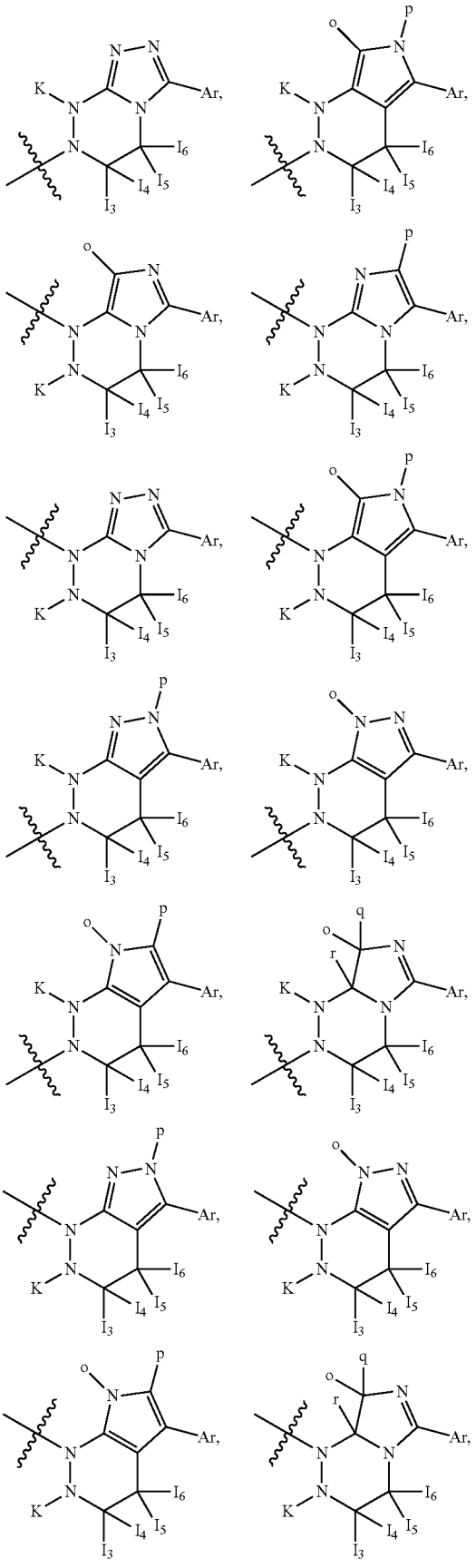

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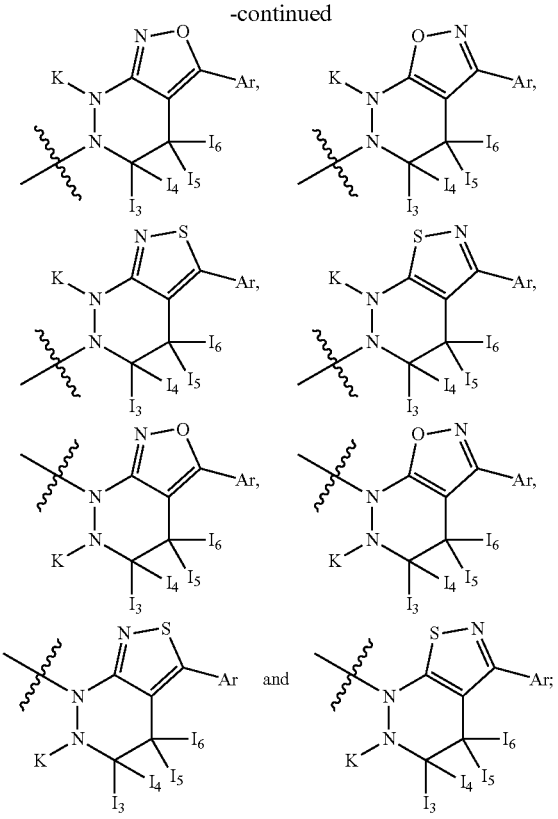


K is selected from the group consisting of hydrogen, hydroxyl, $OR^{54'}$, (C_{1-6})alkyl and (C_{3-7})cycloalkyl;

I_1, I_2, I_3, I_4, I_5, and I_6 are each independently selected from the group consisting of H, halogen, (C_{1-6})alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl, $CR_{81}R_{82}OR_{83}$, COR_{84}, $COOR_{85}$, or $CONR_{86}R_{87}$; wherein each of said alkyl and cycloalkyl being optionally substituted with one to three same or different cyano, phenyl, aryl, heteroaryl, heteroalicyclic, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, primary amine, secondary amine, tertiary amine, ammonium, nitro, thiol, thioether, alcohol, ether, acid, aldehyde, ketone, amide, amidine, guanidine, sulfone, sulfonamide, sulfamide, acyl sulfamide, sulfate, sulfuric acid, sulfamic acid, phosphate, phosphoric acid, boronic ester, boronic acid, squarate, squaric acid, oxime, hydrazine, peroxide, among which ether, peroxide, thioether, secondary amine, tertiary amine, ammonium, ester, ketone, amide, amidine, oxime, hydrazine can be either acyclic or cyclic; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

R_{81}, R_{82}, R_{83}, R_{84}, R_{85}, R_{86}, and R_{87} are each independently selected from the group consisting of H, (C_{1-6}) alkyl, (C_{3-6}) cycloalkyl, (C_{2-6}) alkenyl, (C_{4-6}) cycloalkenyl, (C_{2-6}) alkynyl;

L is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{1-6})alkynyl, (C_{3-6}) cycloalkyl, halogen, cyano, $CONR^{40}R^{41}$, $S(O)_2R^8$, $S(O)_2NR^{40}R^{41}$, $C(O)R^8$, $COOR^8$, tetrahydrofuryl, pyrrolidinyl, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, (C_{1-6})alkynyl, phenyl and heteroaryl are each independently optionally substi-

tuted with one to three same or different members selected from the group G; heteroaryl is selected from the group consisting of furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, triazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl;

M is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are each independently optionally substituted with one to three same or different members selected from the group W; and heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

W is selected from the group consisting of (C_{1-3})alkyl, hydroxy, (C_{1-3})alkoxy, halogen and $—NR^{42}R^{43}$; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogens;

l, m and n are selected from the group consisting of H, halogen, OR^8, CN, $(C_1\text{-}C_4)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl group and Group C; alkyl and $(C_3\text{-}C_6)$ cycloalkyl group optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$;

o and p are selected from the group consisting of H, OH, $(C_1\text{-}C_4)$ alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, $(C_3\text{-}C_6)$ cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, halogen (attached to carbon only), and Group C;

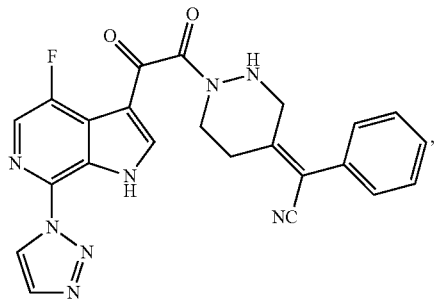
q and r are selected from the group consisting of H, $(C_1\text{-}C_4)$ alkyl optionally substituted with one to three substitutions selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, $(C_3\text{-}C_6)$ cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$ and Group C;

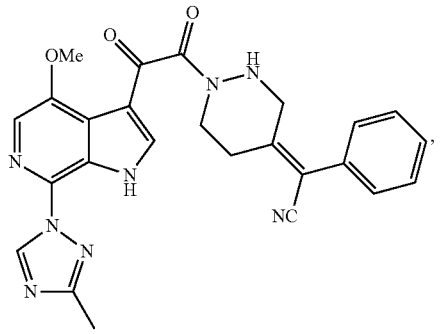
Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl;

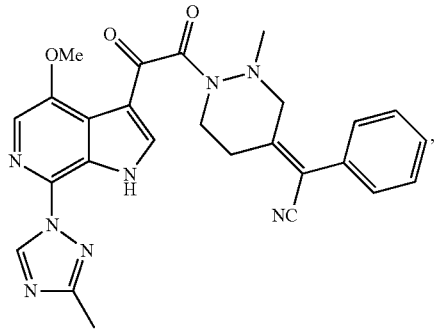
Group C is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group D; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

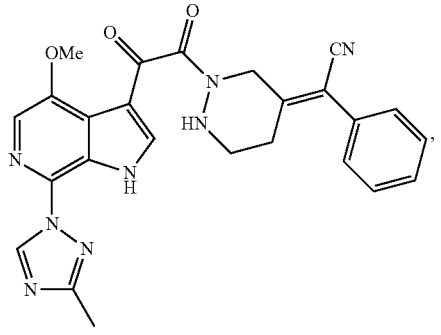
Group D is selected from the group consisting of OH, OR^8, NA^1A^2, CN, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$, $(C_1\text{-}C_4)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR^8, NA^1A^2, $COOR^8$, $CONA^1A^2$, SO_2R^8, $SO_2NA^1A^2$.

2. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:









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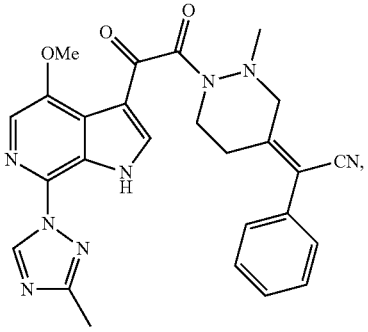

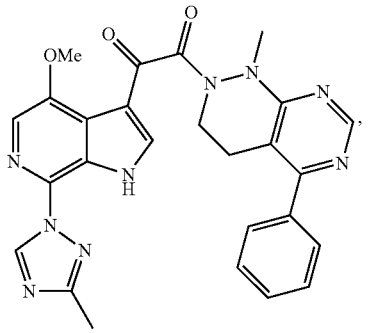

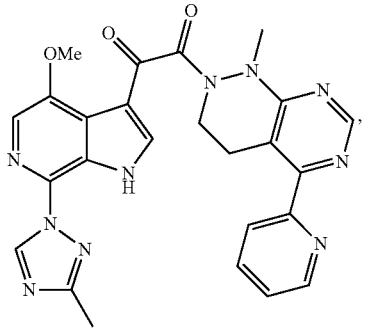

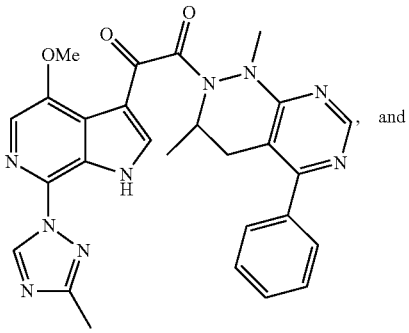

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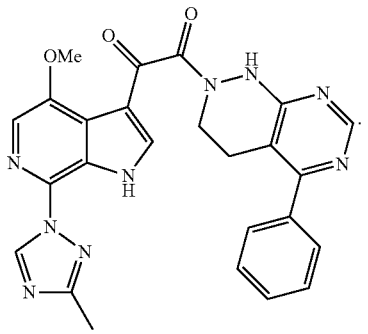
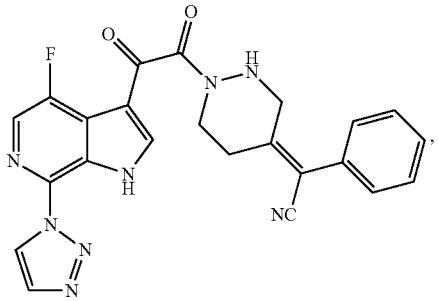
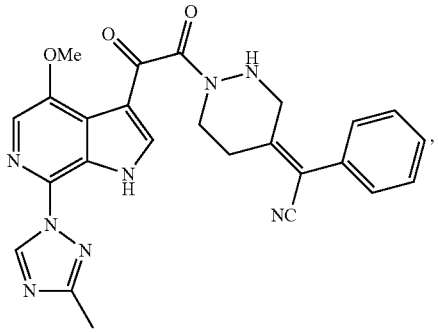
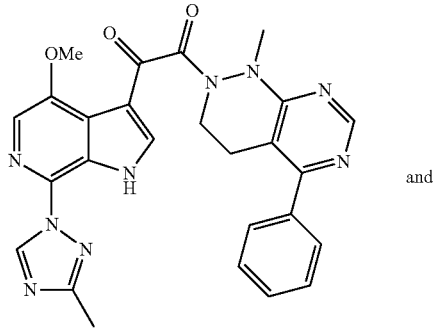


3. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:







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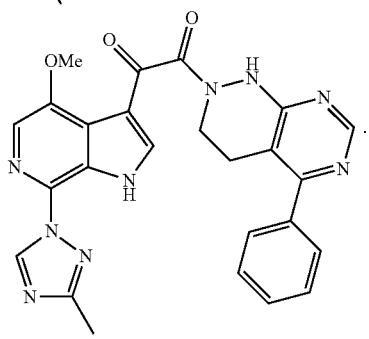

4. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim **2**, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

5. The pharmaceutical composition of claim **4**, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

(c) an immunomodulator; and

(d) another HIV entry inhibitor.

6. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an antiviral effective amount of a compound of Formula I as claimed in claim **2**, and one or more pharmaceutically acceptable carriers, excipients or diluents.

7. The method of claim 6, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and another HIV entry inhibitor.

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